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Effects of Functional Electrical Stimulation Cycling versus Cycling Only on Walking Performance and Quality of Life in Individuals with Multiple Sclerosis: A Randomized, Clinical Pilot Study

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by

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Abstract

Background: Functional Electrical Stimulation (FES) stimulates peripheral nerves via electrical current to evoke muscle contractions and when combined with lower extremity cycling (LE), creates patterned leg movements. Previous studies demonstrated FES cycling is safe and effective in the spinal cord injury and stroke populations with improvements seen in walking speed, muscle mass, and bone density. Few studies have applied FES cycling to a neurodegenerative disorder, such as multiple sclerosis (MS). The aim of this study is to assess the effect of an 8-week training program using FES cycling, compared to Cycling Only, in people with MS (PWMS).

Methods: Using a sample of convenience, PWMS were recruited to participate and randomized to the FES Cycling group or the Cycling Only group. Both groups received training three-times per week for 8- weeks using a LE ergometer. Scores on the 6 Minute Walk Test (6MWT), Times 25-Foot Walk Test (T25FW), Five Times Sit-to-Stand (5XSST), and Timed Up and Go (TUG), and spatiotemporal measure of gait were collected at baseline, (before the 1st session), 4-weeks (before the 13th session), 8-weeks (after the 24th training session), and at 4-week follow-up. Scores on the MS Quality of Life-54 (MSQOL), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Walking Scale-12 (MSWS-12), and Activities-specific Balance Confidence Scale (ABC) were collected at baseline, 8-weeks, and at 4-week follow-up.

Results: Fourteen participants (8 female, 6 male, mean age = 53.64 ± 10.16 years; Patient Determined Disease Steps (PDDS) mean = 3.71 ± .091) completed the training. Cycling power output significantly increased in both groups over time (FES Cycling, $p = 0.03$; Cycling only $p = 0.004$), but no differences were found between groups ($p = 0.08$). The Cycling Only group demonstrated a slightly larger effect size for power output than the FES Group ($d = 0.72$ vs. 0.66). Immediately after the intervention period, scores on the 6MWT, 5XSST, and MFIS, and subscores of the MSQOL-54 improved significantly, but changes did not consistently favor one group over the other ($p > 0.05$). There were no significant differences between groups on any of the outcome measures.

Conclusions: FES Cycling or Cycling Only may be an effective intervention for improving walking endurance, sit-to-stand, and QOL in PWMS. This unique pilot study compared FES cycling versus Cycling Only for PWMS using a customized progression protocol. Further research with larger sample sizes are needed to better understand the effects of FES Cycling on PWMS.

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CHAPTER 1

Background and Overview

Multiple Sclerosis (MS) is a chronic inflammatory disease in which the immune system attacks the central nervous system.[1] There are 2.3 million cases of multiple sclerosis (MS) worldwide with approximately 1 million individuals living with MS in the United States. It is the most common neurodegenerative disease found in developed countries, with a prevalence of 1 in 800. The disease is two to three times more common in women than in men, and is commonly diagnosed between 20 and 50 years of age.[2,3]

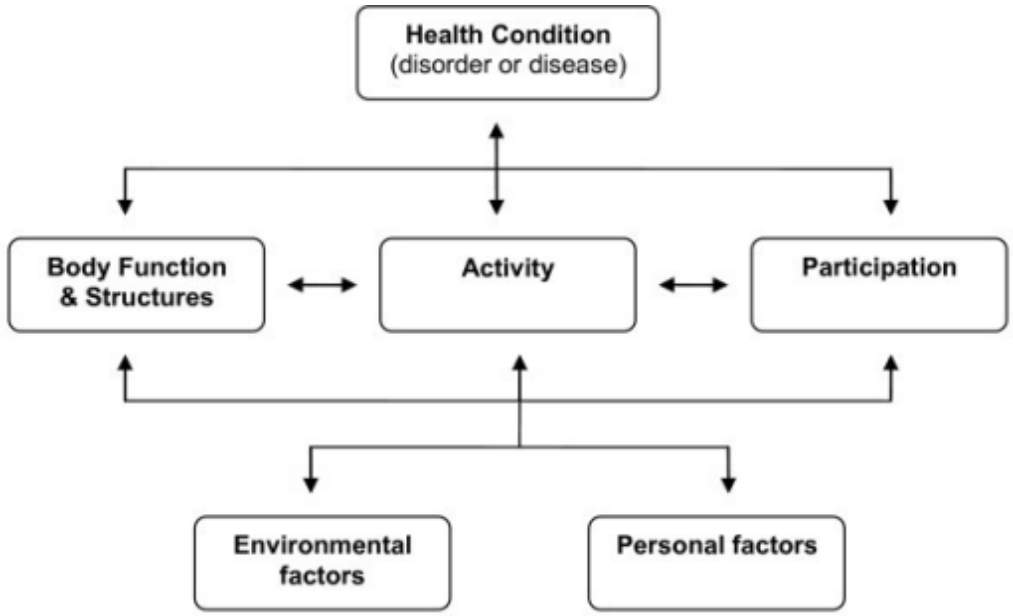
During the disease process, the myelin sheaths that protect nerve fibers and facilitate nerve conduction velocity are damaged and, as a result, transmission of nerve impulses between the brain and spinal cord become impaired.[2] Four clinical courses of MS have recently been redefined by a panel of experts as: clinically isolated syndrome (CIS), relapsing-remitting multiple sclerosis (RRMS), secondary-progressive multiple sclerosis (SPMS), and primary-progressive multiple sclerosis (PPMS).[4] Table 1-1 provides characteristics and descriptions of each clinical subtype.[2] The most common form of the disease is RRMS, but by six to ten years after onset, a large percentage of individuals who were diagnosed with RRMS become classified as SPMS.[3] This change occurs when individuals start to develop steady worsening of the disease with only minor recoveries or plateaus.[3]

Table 1-1 Classification of MS Clinical Courses[4]

Clinical Subtypes	% of MS cases	Description
Clinically Isolated Syndrome (CIS)	Not available	First clinical presentation (lasting > 24 hours) of the disease that displays characteristics that could be MS
Relapsing-remitting MS (RRMS)	85-90%	Acute attacks followed by complete or incomplete recovery
Secondary progressive MS (SPMS)	Not available	Steady worsening of individuals with RRMS. Individuals experience minor recoveries or plateaus
Primary-progressive MS (PPMS)	10%	Slow but progressive neurologic decline from onset with no relapses or remissions

MS is a complex disease due to the wide range of clinical courses and heterogeneity of symptoms. MS can affect an individual's function at every level of the International Classification of Functioning, Disability and Health (ICF) Model, including body function and structure, activities, and participation (Figure 1-1).[5] Changes in body structure and function that commonly occur in people with MS (PWMS) include muscle weakness or paralysis, spasticity, fatigue, incoordination, intention tremor, paresthesias, dizziness, ataxia, visual disturbances, impairment of bowel and bladder functions, cognitive dysfunction, sexual dysfunction, pain, spasms, speech and swallowing disturbances, and emotional changes.[6] When changes in body structure and function persist, it often leads to changes in activities such as transfers, ambulation, and stair negotiation. In turn, these limitations can affect an individual's ability to participate in her or his life roles in the home, work, and community.

Figure 1-1 International Classification of Function, Disability and Health (ICF) Model



The role of exercise can have a significant impact on quality of life (QOL), activity, and participation in persons living with MS.[7,8] A 5-year longitudinal study that tracked the effect of exercise on functional limitations and quality of life revealed that those who exercised more frequently experienced less functional limitations and a higher QOL compared to those who exercised less frequently.[5] In addition, those who demonstrate higher levels of cardiorespiratory fitness, have been shown to have improved cerebrovascular function, improved cognitive task performance, and improved recruitment in certain areas of the cerebral cortex.[9]

Due to the heterogeneity of the disease, rehabilitation professionals utilize a variety of approaches and interventions to treat the changes in body structure and function, activity limitations, and participation associated with MS. Approaches such as resistance training,[10,11] aerobic training,[12] aquatic therapy, [13] yoga,[14] cycling,[15,16] and body

weight supported treadmill training (BWSTT)[17,18] have all demonstrated promising results in targeting a variety of impairments and limitations. In a time where healthcare dollars are being stretched and cost containment is on the forefront, therapists need to be time efficient while prescribing the most effective interventions. Interventions that target multiple body structures, while addressing activity limitations, participation, and QOL, may promote efficiency and effectiveness. The use of an intervention that combines resistance and aerobic training, such as cycling, while providing a repetitive motion may be an effective tool for enhancing function in PWMS.

Functional Electrical Stimulation (FES) is a rehabilitation tool that stimulates intact peripheral motor nerves via electrical current evoking muscle contractions for the purpose of assisting functional movement.[19] It has been utilized in patients with paralysis or weakness due to upper motor neuron lesions.[20] The use of FES in rehabilitation dates back to the early 1960's with the use of a heel switch that triggered short bursts of electrical stimulation to the peroneal nerve resulting in ankle dorsiflexion.[21] It is now used to supplement or replace lost function due to neurological dysfunction and can be applied to assist individuals with activities such as reaching, grasping, walking, and cycling.[22]

FES, combined with lower extremity (LE) cycling, creates a patterned movement of the legs and assists individuals with impaired voluntary control of their muscles in completing the cycling task. It has been utilized in a wide variety of patient populations including, but not limited to, spinal cord injury (SCI), stroke, traumatic brain injury (TBI), Parkinson's disease (PD), Cerebral Palsy (CP), and MS. Studies on the effectiveness of FES LE cycling conducted in the stroke and SCI populations have demonstrated improvements

in gait velocity[23], balance,[24] LE muscle strength,[25] LE muscle mass, [26] aerobic capacity,[24,27] LE bone density,[28,29] and LE range of motion,[30] as well as a short-term reduction of muscle spasms.[22] For PWMS, several studies have documented the use of electrical stimulation for single muscle groups,[33–38] but few studies have applied it to multiple muscles using a FES cycling training paradigm.

PWMS receive traditional rehabilitation, which includes physical therapy, during the course of their disease, but there is a lack of consensus regarding optimal interventions and exercise dosage.[39] FES cycling is utilized clinically for PWMS and according to a company that specializes in FES technology and training, approximately 3-5% of their FES users are PWMS, which translates to approximately 2,000 people (e-mail communication with Scott Simcox, Restorative Therapies, January 12, 2018); however, there is a limited amount of research regarding dosage and effectiveness of FES cycling in PWMS.

Previous studies regarding FES cycling for PWMS have been conducted on individuals with greater disability levels than those proposed in this study, and few measured the impact of this rehabilitation tool on quality of life.[36–38,40–42] Several studies had methodological weaknesses including a lack of a sufficient number of subjects, detail regarding dosage choices, a comparison or control group, and/or a customized progression protocol. These studies will be discussed in detail in a review of the literature in Chapter 2. The purpose of this study was to determine the benefits of FES cycling versus cycling without FES on walking performance and quality of life in PWMS.

Statement of the Problem

Previous studies have demonstrated FES cycling is a safe, feasible, and effective exercise intervention for non-progressive neurological disorders,[23,36,43,44] but only a few studies have applied this intervention to a neurodegenerative disorder, such as MS. These individuals have similar impairments and activity limitations compared to individuals with non-progressive disorders such as SCI and stroke, yet there is lack of evidence to support the use of FES cycling for PWMS.

The purpose of this study was to assess the immediate and short-term effects of an 8-week LE cycling program on walking performance and QOL for PWMS. The goal of this study was to examine if FES cycling is more effective than cycling alone. The groups were compared during training, after training, and one-month post-training to determine if there were changes in walking endurance, spatiotemporal gait characteristics, ability to transition from sit to stand, and quality of life.

Relevance and Significance of the Study

The concept of neuroplasticity after brain damage is well accepted in neuroscience. This current study used the theoretical framework proposed by Kleim and Jones[45] regarding principles of experience-dependent neural plasticity as they apply to PWMS. Kleim and Jones discuss ten principles of neuroplasticity, and several are relevant to the work in this study.[45] Principles outlined in their paper related to the current investigation include: "use it or lose it," "use it and improve it," "repetition matters," and "intensity matters."[45] "Use it or lose it" speaks to the idea of loss of specific brain functions and functional degradation if specific inputs are not provided to the body and "use it and improve it" refers to the idea that training specific functions can lead to improvement in

that function.[45] Kleim and Jones discuss that repetition at high intensities are necessary to induce plasticity.[45]

The evidence regarding the relationship between task-specific exercise and positive neuroplastic changes in the central nervous system[46,47] is mounting. Specificity of training would dictate that in order to improve walking, one would need to train walking, but this type of activity is often not safe at high intensities for PWMS because of the challenges it poses to one's balance and postural control. Finding a rehabilitation intervention that individuals of varying disability level can benefit from is crucial to the process.

It has been hypothesized that cycling has its own set of underlying neural mechanisms, which are repetitive in nature, and similar to the concept of central pattern generators for walking and upper extremity coordination.[48] This could imply that cycling may have some carryover that would help to improve walking performance. This study measured walking outcomes (including endurance, gait speed, and spatiotemporal walking parameters), further exploring this hypothesis. Cycling has been shown to have positive effects on quality of life, walking distance, walking speed, and fatigue, and can be safely applied at moderate intensities in PWMS.[12,15,49]

In PWMS, physical exercise has beneficial effects on aerobic capacity, upper and lower extremity strength, balance, fatigue, and depression.[15,50,51] Based on the available research, Dalgas, Ingemann-Hansen, and Stenager[52] suggest that both resistance and endurance exercises are safe and beneficial for PWMS that have an Expanded Disability Severity Scale (EDSS) score of less than 7. EDSS scores from 0 to 7 encompass a large range of disability and include those individuals with a normal neurological exam

(EDSS=0) to those who require constant bilateral assistive devices to walk about 20 meters without resting (EDSS= 6.5).[53] Dalgas et al[52] report that programs should be designed by professionals and tailored to the individual's capabilities, and lower extremity exercises should have high priority. In addition, studies support that low to moderate intensity endurance exercises are well tolerated by PWMS without any adverse long-term side effects.[50,54]

Cycling on a typical exercise bike is an effective way for PWMS to exercise.[15,55] The results of a pilot study on PWMS (EDSS 4.0 - 6.0) showed bi-weekly cycling for 30 minutes for 12 weeks produced significant improvement in the 6 Minute Walk Test (6MWT) and improved outcomes on the Guys Neurological Disability Index.[49] In a larger randomized controlled study, progressive cycling, combined with balance exercise, was found to be effective for PWMS compared to those performing home-based LE balance and strengthening exercises.[15] Individuals who performed a bi-weekly program of progressive cycling and balance for 8 weeks, demonstrated a significant change in a timed 10 meter walking test (10MWT), total duration of exercise, tolerated maximum workload, Timed Up and Go (TUG), Dynamic Gait Index (DGI), Functional Reach (FR), Fatigue Severity Scale (FSS), Falls Efficacy Scale, and Beck Depression Inventory (BDI).[15] Although the findings of these studies were positive, researchers failed to measure retention of gains after the training period was completed.

FES cycling may be an effective way for PWMS to safely exercise while having a positive effect on gait speed, aerobic capacity, function and quality of life (QOL). In addition, the use of this technology may motivate an individual to engage in physical activity because the cycle provides real-time visual feedback. Once a patient is familiar

with FES cycling, they can perform it as part of a wellness program in the clinical setting or in the privacy of their home. The cycle being used in this study allows the therapist to monitor progress and change parameters remotely.[15] In a study examining the perceived barriers to exercise, physical exertion and limited access to exercise locations were listed as the greatest barriers to exercise in PWMS.[56] Since cycling is performed in a seated position, it is safe for individuals with balance deficits due to their inability to perform activities safely in a standing position. Over time, this treatment paradigm could potentially save money and time not only for PWMS, but also the healthcare system. FES cycling could be utilized in the home environment and may be fully or partially covered by medical insurance. In the past 10 years, FES home-based cycling has been successfully utilized in patient populations such as SCI[36,57] and CP.[58]

Research Questions and Hypotheses

Research Question 1

Is there a difference in aerobic capacity as measured by the 6 Minute Walk Test (6MWT) between FES Cycling and Cycling Only training in PWMS?

Research Question 2

Is there a difference in gait speed as measured by the Times 25-foot Walk Test (T25FW) between FES Cycling and Cycling Only in PWMS?

Research Question 3

Is there a difference in functional lower extremity strength as measured by the 5 Times Sit-to-Stand (5XSST) between FES Cycling and Cycling Only in PWMS?

Research Question 4

Is there a difference in functional mobility as measured by the Timed up and Go (TUG) between FES Cycling and Cycling Only in PWMS?

Research Question 5

Is there a difference in spatiotemporal components of gait between FES Cycling and Cycling Only in PWMS?

Research Question 6

Is there a difference on quality of life and self-reported walking and balance measures between FES Cycling and Cycling Only in PWMS?

Summary

MS is a disabling neurodegenerative disorder that can result in severe disability affecting every facet of an individual's life, creating a financial burden on the individual, family, health care system, and society.[59] It is important for clinicians and people living with MS to have a variety of safe and effective tools to treat individuals with this long-term, progressive disease. Due to the lack of research on the use of FES cycling in PWMS, this study compares the effectiveness of FES cycling to cycling alone, using a variety of objective and subjective measures that span the ICF model and are easily applied in contemporary clinical practice.

Definition of Terms

1. Functional Electrical Stimulation (FES)- when a functional component, such as cycling, walking or reaching, is added to electrical stimulation.
2. FES cycling- a therapeutic intervention that activates LE muscles in a sequential pattern to produce a cycling motion.
3. Fatigue- a perceived lack of physical and/or mental energy that may interfere with

usual and desired activities.[60]

4. Amplitude (mA)- is the current rate of electricity flow.
5. Pulse width (μsec)- is the application of current over brief periods of time.
6. Frequency (Hz)- the number of waves that pass a given point per second.
7. Ramp- time it takes for current to go from zero to maximum amplitude.
8. Training Period- time period from baseline to post-training.
9. Retention Period – time period from post-training to one-month post training.

CHAPTER 2

Introduction

MS is a chronic progressive neurological disease that destroys the myelin that insulates axons in the central nervous system, which affects the transmission of electrical impulses along the axon, slowing nerve conduction.[2] A variety of pharmacological treatments are available to slow the progression of the disease and to treat MS-related symptoms.[61,62] In addition, there are a wide variety of rehabilitation techniques, exercise regimens, and treatment modalities that physical therapists prescribe to help manage MS symptoms and assist individuals in maintaining a physically active lifestyle throughout the disease process.

Over the past 20 years, FES cycling has been utilized in a variety of neurological populations, but research studies have been limited to mostly non-progressive disorders. There is a paucity of FES cycling literature in the MS population, but the available studies have established that this device is safe to use in PWMS. Currently, there are no randomized comparative studies examining the effectiveness of FES cycling for PWMS. In addition, there is a lack of literature regarding dosage including: duration, frequency, treatment progression, and electrical stimulation parameters for FES cycling for PWMS. This study is unique in that it utilized a customized interval training treatment progression, based on baseline submaximal exercise testing and a standardized progression protocol, over an 8-week period for a total of 24 sessions.

Impact of MS

Common activity limitations among PWMS are gait and balance disturbances, including falls.[63] People with MS report a fall incidence of greater than 50% and this increases as individual's age and the disease progress.[63,64] When a large group of PWMS were surveyed, the activities with which they reported frequent falls included: transfers, ambulation, standing activities, stairs/curbs, and exercise/physical activity.[63]

When comparing 2 groups of PWMS, fallers vs. non-fallers, measures that distinguished between these two groups include the 6MWT, TUG, and sway velocity.[64] When comparing PWMS who had minimal disability in gait to matched healthy controls, those with MS demonstrated significant differences in several spatiotemporal gait parameters including: gait velocity, step length, cadence, base of support, step time, and double support time.[65,66] Those with MS also demonstrated greater intra-individual variability with regard to step time and single support time when compared to healthy individuals.[65] Individuals with mild to moderate (EDSS 2.5 – 6) disability demonstrated impairments in gait speed and spent a greater amount of time in the double-support phase of gait compared to healthy individuals.[67] These studies support the use of spatiotemporal gait parameters to detect subtle, yet important changes in gait and to measure the effect of physical therapy interventions on gait performance.

MS-related fatigue is reported in approximately 65% of PWMS.[68] The MS council[60] published a consensus definition of MS-related fatigue as a "subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities." Fatigue can be related to the disease or due to secondary factors including depression, pain, sleep disturbances, medications, and deconditioning.[69] In a

study of individuals with MS (mean EDSS 4.07 ± 2.28) detailing the effect of depression, fatigue, and disability on quality of life, the authors found that fatigue was strongly associated with a low score on the physical and mental health composite on the MSQOL-54 ($r= -.66$, $P<.0001$; $r= -.69$, $P<.001$, respectively).[70] In addition, a step-wise regression model showed that fatigue is a significant predictor (67%) of quality of life.[70]

Exercise and MS

Exercising and living an active lifestyle are beneficial to PWMS.[7,71] Individuals with greater disability in ambulation tend to achieve less than the recommended daily activity levels when compared to those individuals without ambulation limitations.[72] Individuals who exercise often report a decrease in the perception of fatigue.[73] Improvements in fatigue outcome measures have been reported in a variety of exercise types, including high-intensity resistive exercises,[74,75] yoga,[14] and endurance/aerobic exercises.[54] In addition, physically active PWMS monitored by accelerometers reported lower levels of disability, depression, fatigue, and pain.[76]

In an animal model training study in which an autoimmune encephalopathy similar to the disease process in MS was induced, researchers demonstrated that endurance type exercise may serve to slow the disease progression and reduce the length of exacerbations.[77] Other experts have suggested that exercise may serve to protect,[78] regenerate, and adapt neuronal processes that can reduce long-term disability.[46] Proteins such as nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF) may have an impact on progressive diseases such as MS and may play a significant role in the neural regenerative process. In a study by Gold et al[78] investigators reported statistically

significant increases in NGF and BDNF serum concentration levels, in PWMS (EDSS mean of 2.3 ± 0.2), after only one, 30-minute session of cycling. However, due to the short training duration, no conclusions could be made regarding the effect of exercise on neural plasticity from this study. In a more recent randomized control trial in PWMS, researchers compared an exercise group to a sedentary group and found significant changes in BDNF after 24 sessions of endurance and resistance training.[79] In contrast, despite the authors' hypotheses that serum concentrations levels of NGF and BDNF would be elevated after a training protocol using a traditional bicycle, no changes in BDNF or NGF were found in PWMS after an 8-week, two times per week, 30 minute intervention.[80] Interpretation of this study should be approached with caution since the exercise protocol may not have been intense or long enough in duration to induce long-term changes in neurotrophic factors. Findings did support significant changes in quality of life, physical fitness or coordination.[80]

It is a challenge for PWMS to pursue an active lifestyle and exercise prescription is not well utilized in this population.[81] A variety of interventions have been used that target resistance training, endurance training, or combined training. Aerobic training can include treadmill training, arm and/or leg ergometry, aquatic therapy, and yoga. Individuals who participated in aerobic training programs demonstrated improvements in physical fitness, activities of daily living (ADL), mood, and fatigue.[50] When further examining aerobic training studies, the duration and frequency of training sessions vary considerably. Training sessions ranged from 1-5 days/week[14,49,71] for periods of 2 - 26 weeks.[14,82] A sample of studies that utilized cycling as part of the training intervention also present with a wide range of frequencies and durations, ranging from 2 times per week for 8-weeks,[50] 2 times per week for

12-weeks,[49] 5 times per week for 3-4 weeks,[71] 3 times per week for 24-weeks,[83] 3 times per week for 15-weeks,[50] and 4-5 times per week for 16-weeks.[84] Frequency and durations as little as 2 times/week for 8-weeks have shown improvements in quality of life and lower blood lactate levels, indicating training effects.[80]

When further examining the resistance training studies, the range of duration and frequency of training sessions varies considerably. Training sessions ranged from 2-7 days/week[85,86] for periods of 8-10 weeks.[87,88] Improvements in muscle strength and functional capacity in individuals with RRMS (EDSS between 3.0 and 5.5) have been reported after a 12 week, bi-weekly, lower extremity strengthening program that included a five minute warm-up on a stationary bicycle and five lower extremity exercises.[10] Functional capacity testing included a variety of measures, such as a chair stand test, stair-climbing test, 10MWT and 6MWT, and significant improvements occurred in all measures and continued improvements were documented at post-testing follow-up at 24 weeks.[10]

Cycling and MS

Cycling is a safe and effective method of exercise for PWMS.[15,49] A small pilot study by Kileff and Ashburn[49] assessed the effects 30 minutes of cycling during a 2 times per week, 12 week cycling program. This study included people with moderate disability (EDSS 4.0 – 6.0) and outcomes were favorable with subjects demonstrating an improvement in their 6MWT and Guys Neurological Disability Scale scores.[49] Improvements were not observed in the 10MWT and Functional Reach (FR) test, which is not surprising since gait speed and balance training were not the focus of the training.[49]

In a randomized controlled study by Cakt et al [15] progressive cycling, combined with balance exercises, were found to be more effective for individuals with RRMS and SPMS compared to a group performing home-based balance and strengthening exercises.

Collet et al[16] performed a cycling study that examined outcomes using three different protocols. Subjects in all groups participated in 20 minutes of cycling, two-times per week. Subjects were randomized into one of three groups: continuous cycling (at 45% peak power), intermittent cycling (30 seconds cycling/ 30 seconds rest at 90% peak workload), or combined cycling (10 minutes intermittent at 90% peak workload and 10 minutes continuous at 45% peak workload). Outcomes were measured at the halfway point at 6 weeks, at the end after 12 weeks, and follow-up at 24 weeks.[16] Investigators found significant differences in 2 minute walk test (2MWT) after 6 weeks of cycling (6.96 ± 2.56m, 95% CI: 1.81 – 12.10, Effect size = 0.25, $p < 0.01$) and no significant increase in this outcome from 6 to 12 weeks.[16] When all participants were combined for analysis, a repeated measures analysis of variance (repeated measure ANOVA) revealed significant and positive changes in both the 2MWT and TUG, and leg power ($p <0.01$, $p< 0.05$, $p<0.05$ respectively) at the 6 week mark. Interestingly, no further improvements in the 2MTW and TUG were seen at 12 weeks, but leg power continued to demonstrate significant improvements ($p<0.01$).[16] At 24 weeks (12 weeks after the training period) significant decreases were seen in the 2MTW, TUG, and leg power indicating detraining.[16] Based on the between groups analysis, participant attendance, and adverse events, the authors recommended that low-intensity continuous cycling may be the safest approach for PWMS, noting that further study with larger samples and different dosages needs to be

performed.[16] Based on Collett et al's[16] study it appears that changes in endurance occur earlier in training than changes in strength.

Functional Electrical Stimulation

Neuromuscular electrical stimulation (NMES) provides stimulation at frequencies ranging from 20-50 Hz and assists skeletal muscles in producing a tetanic muscle contraction by stimulating intact peripheral motor nerves.[19,89] It has been applied to patients with paralysis or weakness due to upper motor neuron lesions and is commonly utilized in patients with stroke, SCI, CP, and MS.[20–22,33,34,58]

Several studies have documented the use of electrical stimulation for single muscle groups in PWMS with variable success.[33–35] Chang et al[33] found that PWMS reported reduced perceived fatigue as measured by Modified Fatigue Impact Scale (MFIS) scores after surface FES treatment was applied to the quadriceps muscles. Subjects were in a seated position and were instructed to avoid actively engaging in the movement or task. In PWMS who presented with foot drop, Barrett et al[34] compared passive FES applied to the peroneal muscle to a home exercise program (HEP) that included LE strengthening and stretching, seated balance activities, and standing balance activities. The exercise group demonstrated a greater improvement in walking speed and distance compared to the FES group.[34] This study supports the use of FES as an adjunct to active therapy for use in PWMS.

A randomized control study in PWMS by Broekmans et al[35] compared resistance training, with and without electrical stimulation to the quadriceps, and found no significant difference between muscle strength gains between groups after 20 weeks of resistance training that consisted of unilateral leg press, leg extension, and leg curls. In

addition, there were no gains in functional mobility as measured by the TUG, Timed 25-Foot Walk (T25FW), 2MWT, Functional Reach, and Rivermead Mobility Index.[35] The quadriceps were the only muscle groups stimulated in this study and were only stimulated during the exercises. The selected outcome measures may not have been the appropriate choices to capture a change in function since improvement on these measures are unlikely to be due to changes in muscle strength of a single muscle group.

When functional movement is paired with electrical stimulation, it is referred to as functional electrical stimulation (FES).[21] FES has evolved over 50 years from the simple heel switch and is now routinely used to supplement or replace lost functional mobility due to neurological impairment during a variety of activities.[22] In the 1980s, the combination of cycling using FES was introduced[90] and is now most known for being used by individuals with SCI. However, research studies support the safety and efficacy in other neurological populations including CVA,[23,43] CP,[57] and MS.[36]

FES cycling using an ergometer combines the technology of electrical stimulation and cycling. This device contains software that delivers stimulation during cycling and is designed to stimulate multiple muscle groups at the appropriate time in the cycling pattern to produce a smooth cyclical motion. The selection of stimulation parameters, cycling speed, and resistance can be customized to each patient's tolerance and fitness level. In addition, the ergometer allows clinicians and researchers to measure specific outcomes during cycling, including the amount of work (power output), distance traveled, and asymmetry during cycling.

FES Cycling in Neurological Populations

FES cycling has been studied in individuals with SCI more than any other neurological diagnosis. Exercise adherence rates for home use of FES cycling in lower extremities for people with SCI ranges from 62%[91] to 82%[92,93] in published case reports. These studies ranged in length from 6-weeks to 1-year. Studies show benefits in multiple body systems including, cardiovascular, integumentary, and musculoskeletal, but little evidence in the SCI literature exists that directly links the use of FES cycling to clinically meaningful functional change in this population due to the level of disability.[94–96] Frotzler et al[29] and Chen et al[28] studied the use of high-volume FES cycling for improving bone density and found significant increases in trabecular and total bone mineral density in the distal femur when the gluteals, quadriceps, and hamstrings were stimulated. In addition, improvements in muscle mass,[26] muscle strength,[93] and muscle fiber composition toward more fatigue resistant fibers were found.[93]

A wide range of cycling time (30 – 60 minutes), frequency (2-3 times per week), and duration (12 – 24 weeks) has been reported in the SCI literature depending on the goal of the study.[26,91,92,96,97] Stimulation parameters regarding frequency, pulse width, and amplitude also vary greatly depending on SCI classification, spasticity, and level of sensation.[26,91,92,96,97]

FES cycling has also been studied in individuals recovering from acute, sub-acute and chronic stroke.[23–25,27,31,43] These studies examined a variety of outcomes including: spasticity,[98] aerobic capacity,[24,27] maximal power output,[23,27] balance,[27] maximal isometric voluntary contractions (MVC),[25] gait velocity,[23,24,43] sit to stand transfers,[23,25] and upright motor and trunk control.[25,43]

Four studies examined the effects of cycling with and without FES.[27,31,43,99] Janssen et al[27] evaluated the effects of FES cycling versus active cycling without muscle provoked electrical stimulation in a group of 12 people with chronic stroke who trained two times per week for 6-weeks with a goal of cycling for a total time of 25 to 30 minutes. Stimulation parameters were set at a frequency of 60Hz, a pulse width of 450μs and amplitude to tolerance. Outcome measures were used to measure aerobic capacity, maximal power output, functional performance, and lower limb muscle strength.[27] Significant improvement occurred in both groups on all measures except for muscle strength, but no differences were found between the two training groups.[27] Researchers need to continue to take a closer look at FES cycling compared to cycling alone to determine optimal dosage and which of these interventions may be most beneficial in the stroke population. In addition, stimulation parameters need to be customized to maximize muscle activation during stimulation.

Yeh et al[31] focused on the effect of FES assisted cycling on spasticity in individuals with sub-acute stroke. Subjects performed 2 sessions of cycling for 20 minutes each, one with FES assistance, the second without. Cycling sessions were separated by at least one day.[31] Findings supported that FES cycling had a greater effect on reducing hypertonia than cycling without FES when measured immediately after the training session. FES parameters were set at a frequency of 20Hz and a pulse width of 300μs, with amplitudes ranging from 0 – 100mA.[31] Investigators did not perform any follow-up to evaluate potential long-term effects.

A larger randomized control study by Ambrosini et al[43] involved subjects with chronic hemiparetic stroke. Thirty-five individuals were randomized into either an FES

cycling group or a placebo FES cycling group.[43] The placebo group performed passive cycling with electrodes applied, but did not receive any stimulation. This was a 4-week, 20 session training study in which each session lasted up to 25 minutes. FES parameters were set at a frequency of 20Hz and a pulse width of 300μs with the amplitude set to tolerance.[43] Muscles stimulated included the quadriceps, hamstrings, gluteals, and anterior tibialis. The FES cycling group demonstrated significant improvement on the Motricity Index, Trunk Control Test, Upright Motor Control Test, gait speed, and mean work of the paretic leg after training.[43] The placebo group did not demonstrate any significant improvements in outcomes after training.[43] These findings are significantly different than those from Janssen et al,[27] but the patient population and study design were not equivalent, making comparisons difficult. Differences in outcomes of these studies may be attributed to: patient acuity, intensity of the training protocol, duration of training, stimulation settings, and outcome measure selection. One primary difference was that in the Janssen et al[27] study, subjects performed active cycling, whereas the subjects in the Ambrosini et al[43] study cycled passively, with sham stimulation.

Bauer et al[99] extended the work of Ambrosini et al[43] and Janssen et al[27] and evaluated the effects of active cycling with and without FES on balance and gait in a group of 40 individuals with severe hemiparesis due to stroke. Individuals cycled 20 minutes, 3 times per week for 4 weeks at a self-selected speed above 20 rpm.[99] While in the study, subjects also received other interventions during their scheduled physical, occupational, and speech therapy sessions.[99] Individuals in the FES group received stimulation to only the paretic limb with a frequency of 25Hz, a pulse width of 250μs, and amplitude set to tolerance.[99] Significant differences for the FES group were found during the intervention

phase (pre to post-intervention) for the balance portion of the Performance-Oriented Mobility Assessment (POMA) and on the individual's Functional Ambulation Classification (FAC) with both measures revealing moderate to high effect sizes.[99] The authors also measured the effects of the intervention on muscle tone in the quadriceps and hamstrings using the Modified Ashworth Scale (MAS) and found there were no statistically significant differences in either intervention group.[99] The study methodology was similar to Janssen's study[27] in which individuals were actively cycling and the frequency of stimulation was relatively low; greater results may have been seen with higher frequencies and cycling speeds.

Alon, Conroy, and Donner[23] demonstrated improvements in people pedaling power, the TUG, and gait velocity in people with chronic stroke using a 3 times per week, 8-week, 30 minute FES cycling training paradigm using a frequency of 50Hz, a pulse width of 250μs, and amplitude set to tolerance. Subjects in their study cycled at or close to 60 rpm while resistance was gradually increased.[23] Their training was safe and well tolerated by a variety of post-stroke disability levels.

The post-stroke population has several similarities to the MS population in that they both demonstrate volitional movement, partially preserved sensation or hypersensitivity, and asymmetrical movement patterns due to spasticity, weakness or motor control. Based on these similarities, FES cycling may lead to similar benefits in PWMS.

Multiple studies report that PWMS benefit in a variety of ways from resistance and aerobic training.[83,85,100] Exercise equipment that can offer a safe, moderate intensity workout is readily available in the traditional gym environment, but this often is not the

best option for PWMS due to gait or balance difficulties, or the need for assistance. FES cycling can be performed in the home environment with some initial patient education and set-up by a professional. This offers PWMS an exercise option if they do not have the time or ability to travel outside their home, have limited therapy through their insurance, or have financial constraints preventing attendance to wellness programs.

There is a small number of case reports and pilot studies that have examined the efficacy and effectiveness of FES cycling for PWMS.[36,37,40,101] The available FES cycling studies are summarized in Table 2.1. A review of the literature yields no randomized clinical trials or quasi-experimental studies comparing FES cycling to other interventions in PWMS.

Table 2-1 Summary of FES Cycling Studies for PWMS

Study	Sample Size	Disability	Study Design	Main Outcome Measures	Protocol/ Dosage	FES Parameters	Muscles Stimulated	Results
Krause, Szecsi and Straube[37]	1	Non-ambulatory SPMS, EDSS = 7.5	Case Study	MAS and Pendulum Test	2 sessions, 30 min. with 3-5 min. breaks,	Only reported amp - 90mA	Quads, hamstrings, gluteals	Reduction in spasticity immediately post-training.
Szecsi et al[40]	12 (4 drop-outs)	EDSS 4.0 – 8.0	Single-group, cross-over design	Cycling cadence and torque recordings, MAS, MMT, 10MWT	3 times per week for 2 weeks, 6 sessions total, 12-18 total min. of pedaling (6 min. of stimulated pedaling)	PW = 300µsec, Freq = 20Hz, Maximal amp = 127mA	Quads, hamstrings	Power and smoothness improved during stimulated pedaling within session. No significant change over 2 weeks. Short-term reduction in spasticity. No change in MMT or 10MWT.
Ratchford et al[36]	5	PPMS or SPMS, EDSS 6.0 – 6.5 inclusive	Single-group, pilot study	2MWT, T25FW, TUG, leg strength, MSFC	3 times per week, 1-hour sessions, for 6 months (home-based)	PW = 250µsec, Freq = 33 to 45Hz	Quads, hamstrings, gluteals	Improvements in strength of stimulated muscles. Improvements in walking endurance gait speed, and quality of life.

Study	Sample Size	Disability	Study Design	Main Outcome Measures	Protocol/ Dosage	FES Parameters	Muscles Stimulated	Results
Fornusek and Hoang[41]	7	EDSS 6.5 - 8.5, SPMS	Single-group design	Thigh girth, transfer ability and cardio-respiratory response	2-3 times per week, 10 weeks, 18 sessions, progressed to 40 min sessions, passive pedaling at cadence of 10 rev-min	Initial settings: amp = 30mA, increased as tolerated, PW = 300μsec, Freq = 35Hz	Quads, hamstrings, gluteals	Significant increases in thigh circumference, improvement in perceived transfer ability, small increases in cardiorespiratory metabolism.
Hammond et al[102]	40	EDSS 2.5 - 7.5, RRMS, SPMS, PPM,	Retro-spective cohort study	EDSS, ISNCSCI	4.4 hours of therapy per month 15-month period. Protocol not reported.	Parameters not reported	Not reported	ISNCSCI motor scores significantly improved when compared to non-FES users. Stable neurologic function over 15 months.
Backus et al[38]	14	Household ambulation of < 70 feet, Moderate to Severe MS	Single-group design	MFIS, MSQLI, MMT, MAS	3 times week for 4 weeks, 30 min. sessions, 12 sessions, target speed 35 -50 rpm	PW = 200μsec, Freq = 50Hz	Quads, hamstrings, gluteals	Significant decrease in physical and psychosocial subscales of MFIS. Improved cycling times.

Abbreviations: EDSS = Expanded Disability Status Scale, ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury, MS = Multiple Sclerosis, MFIS= Modified Fatigue Impact Scale, MSQLI = Multiple Sclerosis Quality of Life Inventory, MMT = Manual Muscle Test, MAS = Modified Ashworth Scale, MSFC = Multiple Sclerosis Functional Composite, SF-36 =Short-Form 36, Freq = frequency, PW = pulse width, amp = amplitude, min. = minute, 2MWT = 2 Minute Walk Test, T25FW = Timed 25-Foot Walk

Krause, Szecsi, and Straube[37] report a single case study of a non-ambulatory, 46 year-old man with secondary progressive MS with an EDSS score of 7.5. The investigators bilaterally stimulated three muscle groups during cycling: the gluteals, quadriceps, and hamstrings. This individual tolerated 30 minutes of stimulated cycling with short (3-5 minute breaks). He tolerated stimulation amplitudes up to 90mA, but authors did not report the frequency or pulse width. This individual experienced a reduction in spasticity after each of the two training sessions as measured by the MAS and the pendulum test.[37] The authors did not measure spasticity reduction hours or days later, therefore no conclusions can be made regarding the long-term effectiveness. In addition, there were no outcomes or subjective descriptions reported that related this reduction of spasticity to gait, functional, or quality of life.

Szecsi et al[40] examined the effect of FES cycling on biomechanical and functional outcomes. Eight PWMS completed the FES cycling training 3 times per week for 2 weeks for a total of 6 sessions, while also receiving conventional therapy. Training sessions were 12-18 minutes in length and contained stimulation and non-stimulation phases. Although no adverse reactions were reported, four subjects dropped out; reasons provided were: change of schedule, change of medications, failure to comply, and difficulty with transfers due to a high degree of disability. The quadricep and hamstring muscle groups were stimulated in bilateral lower extremities.[40] They utilized a fixed frequency of 20Hz, a maximal amplitude of 127mA, and a fixed pulse width of 300μsec.[40] These settings may not be optimal to elicit strong contractions in all PWMS.[103] Symmetry of pedaling and power output was examined at various stimulation and non-stimulation intervals during the 12 -18 minutes of cycling.[40] Subjects were able to achieve greater

cycling power and symmetry of pedaling with FES than without FES.[40] Functional outcomes were measured both before and after training and included the 10MWT, MAS and Manual Muscle Testing (MMT).[40] There were no significant changes in these measures except for a short-term reduction in spasticity before and after each training session.[40] Subjective feedback from participants revealed reports of increased functional abilities (e.g. transfers, stairs, activities of daily living) and quality of gait, such as improved leg lifting.[40] It is unknown if greater functional improvements would have been revealed if the training period was longer and more intense. The training period in this study was significantly below the exercise recommendations for PWMS. In addition, a frequency of 20Hz is on the low end of what is recommended for FES cycling. A study by Eser et al[103] demonstrated that, in people with motor and sensory incomplete SCI, when pulse width and amplitude were held at a constant, higher frequencies (50 and 60 Hz) elicit larger power outputs.

In a pilot study by Ratchford et al[36] the research team examined the relationship between FES cycling and changes in walking performance, LE strength, and QOL. Four individuals (EDSS 6.0 to 6.5 inclusive) with primary or secondary progressive MS completed the study. Individuals performed FES cycling in the home environment using an FES cycle for 6 months. They were instructed to cycle 3 times per week for one-hour sessions. In addition to looking at impairments and functional measures at baseline, 3 months, and after the 6-month period, researchers also examined the relationship between FES cycling and changes in cytokines and growth factors in cerebral spinal fluid (CSF).[36] Participants were trained to use the FES cycle in their home and started with the same initial settings: a symmetric biphasic waveform, phase duration 250μsec

randomized ± 25%, and a frequency 33 to 45Hz.[36] Electrical stimulation was applied to the quadriceps, hamstrings, and gluteal muscles.[36] There were no serious adverse advents, but one participant reported an increase in spasticity, which was treated by an increase in their spasticity medication.[36] Another participant with a history of irritable bowel syndrome reported increased bowel incontinence, which was remedied by adjustments in this individual's bowel program.[36]

The outcomes of the Ratchford et al study were favorable, but due to small sample size, statistical analysis was not performed.[36] The mean number of sessions per week was 3.8 (range 3.1 -5.1), demonstrating that these individuals were able to tolerate training during the suggested time period.[36] The average power output and cycling mileage from the first two weeks compared to the last two weeks improved from 3.2 watts to 4.6 watts and from 9.9 miles to 10.6 miles.[36] The improvements in the main neurologic measures, the 2MWT, T25FW, and the TUG, were 13%, 36%, and 22%, respectively.[36] Investigators also observed improvements in self-selected walking speed, double support time, and step length coefficient of variation, as measured on the instrumented GAITRite® walkway.[36] Results showed a decrease in pro-inflammatory cytokines and an increase in nerve-related growth factors in the PWMS who performed FES cycling when compared to healthy controls.[36] These preliminary findings suggest that FES cycling may reduce inflammation and promote neuronal repair, along with improvements in clinical outcome measures.[36]

In a retrospective study, Hammond et al[102] reported on 40 individuals who participated in a long-term FES cycling program for 15 months. The sample of subjects had EDSS scores ranging from 2.5 – 7.5 and were distributed across the three main types

of MS (RRMS, SPMS, PPMS).[102] The main outcome measures were the EDSS and the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI). The ISNCSCI is an evaluation tool that examines sensory and motor function as well as anal and perianal function, but has yet to be validated in the MS population.[102] Details regarding duration, intensity, stimulation parameters, and muscles stimulated were not published. EDSS and ISNCSCI scores remained stable over the 15 month periods and in those with PPMS and RRMS and there was a slight decrease in EDSS score, noting improvement in disability, although the changes were not statistically significant.[102] Based on this study, long-term FES cycling use may help to stabilize or prevent disease progression in PWMS.

Fornusek and Hoang[41] investigated the feasibility and stimulation tolerance in seven individuals ranging from an EDSS 6.5 - 8.5. The focus of their study was to individualize stimulation and cycling progression over 18 sessions (2-3 times per week).[41] Individuals were instructed not to actively cycle and to allow the ergometer to passively move their legs at 10 rev-min. Objective outcome measures included pre- and post- thigh circumference and metabolic exercise testing (heart rate, oxygen uptake, and ventilation) using open circuit spirometry.[41] Individuals were also interviewed regarding therapeutic benefits and detriments of the intervention. They were asked to rate the change in their ability to transfer on a 15 point scale where -7 indicated a "great deal worse," 0 indicated "no change," and +7 indicated "a very great deal better."[41] Participants showed significant changes in thigh circumference ($p > .001$) and although improvements in metabolic testing were present, statistical analysis was not performed due to the small sample size.[41] All participants reported a positive change in transfer

ability (median 4, interquartile range 2-5).[41] This study provided evidence that individuals with advanced MS with intact sensation tolerate NMES when it is appropriately applied and gradually increased.[41] Since individuals were not actively cycling, improvements can solely be attributed to the NMES. This study did not explore if the addition of active cycling would impact further improvements in outcomes.

Backus et al[38] completed an FES cycling study to evaluate the safety, cycling performance, fatigue, spasticity, pain, and quality of life on PWMS with severe weakness. Fourteen participants cycled 3 times per week for 4-weeks for a total of 12 sessions with no adverse events.[38] The pulse width was set at 200μsec and frequency at 50Hz. Amplitude was based on the amount of stimulation needed to achieve a target cycling speed between 35 and 50 rpm. Sessions included a 2-minute passive warm-up followed by 30 minutes of active cycling, which was either voluntary or assisted with electrical stimulation, and a 2-minute passive cool-down.[38] Once a participant was able to pedal for 30 minutes while maintaining a cycling speed of 35 to 50 rpm for three consecutive sessions, resistance was then increased by 0.14Nm increments.[38] Investigators performed statistical analysis on the twelve participants who had a positive change in power output and a t-test revealed a significant improvement from pretest to posttest ($p = 0.01$) and a large effect size (Cohen's $d = 1.06$).[38] Data was then analyzed as two sub-groups, those who could not cycle for the entire 30 minutes and those could complete 30 minutes of cycling. Seven of the fourteen individuals could not cycle the entire 30 minutes, but all demonstrated significant increases in active cycling time ($p = 0.04$) and medium-large effect size (Cohen's $d = 0.77$). This group did not show a significant change in power output from pre- to post-training ($p = 0.07$). The other sub-group (those who

could complete 30 minutes of cycling) (n = 7) demonstrated a significant change in resistance ($p < 0.01$), but not power ($p = 0.06$), from pre-to-post training, but effect sizes for resistance and power were both large in magnitude (Cohen's $d = 2.53$ and 5.25, respectively). Muscle strength, spasticity and pain scale outcomes were not significant, however, there was a significant decrease in two subscales on the MFIS (physical, $p = .02$, Cohen's $d = .43$ and psychosocial, $p < .01$, Cohen's $d = 0.74$) and the SF-36 social subscale ($p < .01$, Cohen's $d = 0.90$). There appears to be a strong effect of QOL social subscales, which may be due to the socialization that participants experienced as part of the study.

The results of the FES cycling MS studies described above only stimulated proximal muscle groups,[36–38,40,41,101,102] omitting muscle groups such as anterior tibialis or gastrocnemius musculature, both of which are integral for efficient gait. The anterior tibialis is the primary muscle utilized for clearing the foot during heel strike and swing, and the gastrocnemius plays an integral role in the propulsion of gait during swing phase; both of these muscle groups can be effected in PWMS.[104]

The present study compared FES cycling to Cycling Only in PWMS. Based on a review of the literature, the dosage of FES cycling and Cycling Only groups was selected to be 3 times per week, for 8-weeks for a maximum of 45 minutes per training session. Since weakness often occurs in multiple muscle groups, stimulation was applied to both LEs and five muscle groups, including the gluteals, quadriceps, hamstrings, anterior tibialis, and gastrocnemius. An individualized interval-training progression protocol was employed and is described in detail in the methodology.

Electrical Stimulation Parameters

Activation of motor units during voluntary contractions are recruited from small (Type I, slow twitch, very fatigue resistant), to intermediate (Type IIa, fast-twitch, fatigue resistant), to large (Type IIb, fast twitch, fatigable) motor units, as demands for force are increased (Henneman's size principle).[19] When using NMES, it was originally thought that recruitment of motor units occurred from the largest to smallest motor units as stimulation intensity increased, but this has been disproven by several studies.[19,105] It is currently accepted that when using NMES, muscles are activated non-physiologically, in a random, non-selective manner,[105] which can lead to decreased efficiency of muscle contractions and neuromuscular fatigue.[89] It has been suggested that this decreased efficiency may be due to non-physiologic motor recruitment[89] and/or poorly timed biomechanical factors.[106] These challenges also apply to FES cycling, but strategies can be employed to offset the high degree of fatigue that can occur with FES.[89] Hunt et al[106] suggests that the timing of muscle activation needs to be optimized, as well as investigating alternative stimulation strategies such as varying the stimulation patterns and frequency settings. In addition, it has been suggested that customization of stimulation parameters can reduce fatigue and improve power output.[89]

In FES cycling, efficiency and power output have been found to be lower when compared to volitional cycling.[107] In a study comparing volitional and electrically stimulated cycling in a group of able-bodied subjects, the mean metabolic efficiency of volitional cycling versus FES cycling was 29.8% and 16.4% respectively.[106] FES cycling efficiency in people with impaired sensory and vasomotor pathways has also been found to be slightly lower than FES efficiency when compared to anesthetized able-bodied

individuals.[108]

This current study was limited to the waveform and muscle activation patterns that are pre-set by the RT300 cycle (RT300, Restorative Therapies, Inc., Baltimore, MD). The RT300 cycle delivers electrical stimulation to peripheral nerves of selected muscles in coordination with crank rotation, and alterations cannot be made in the timing of muscle activation within the cycling motion.[109] The selection of stimulation parameters influences FES cycling performance and should be set by trained clinicians with knowledge of FES and MS. Electrical stimulation may induce discomfort in individuals with intact or partial sensory and motor paresis, so it is crucial that clinicians adjust stimulation parameters accordingly. The RT300 Sage Stimulation Controller allows the clinician to alter the stimulation parameters throughout a treatment session depending on the patient response, comfort, and treatment goals.[109]

PWMS present with some challenges due to issues with skin hypersensitivity, spasticity, and fatigue, but adjustments to stimulation parameters can be made to minimize these challenges.[89] In this current, study the selection of the starting stimulation levels were based on the primary investigators (PI) clinical experience, coursework completed on FES cycling, clinical electrophysiology principles, and recommendations from Restorative Therapies, Inc. based on their current database on PWMS who use their cycle for training. Based on a database review by Restorative Therapies Inc., a frequency of 43.5 Hz was suggested as the optimal frequency and to be held at a constant (oral communication with T. Ann McElroy, January 30, 2014). Muscle stimulation frequencies typically range from 20-50Hz,[89] and higher frequencies tend to be more comfortable due to the smoothing effect of the pulses.

A strong muscle contraction is obtained by adjusting the amplitude and pulse width.[19] The starting pulse width was 250μsec and amplitude was adjusted in a systematic manner to optimize participant comfort and maximize agonist cross-sectional contraction without stimulating the antagonist muscle or causing a noxious reaction. Robinson and Snyder-Mackler[19] note that small increases in stimulation can cause a large increase in the force of the muscle contraction and therefore stimulation should be slowly adjusted. In this study, the amplitude was adjusted for each muscle group individually, while recognizing that it may take several minutes and/or sessions to increase participant tolerance to stimulation.

Summary

Based on a review of the FES cycling literature in neurological populations, FES cycling may be an effective tool for PWMS to exercise while improving function and quality of life. The published studies in PWMS have not been large enough to draw any definitive conclusions regarding the efficacy of this exercise intervention compared to cycling alone. This is an area that needs to be explored since cycling is performed in a seated position, is safe for individuals who exhibit balance deficits that limit their ability to perform activities in standing position, and can be performed in the home environment.

CHAPTER 3

Introduction

This chapter outlines the research design and methodology used in this intervention study. The specific procedures, protocols, data safety monitoring, resources, and scheduling procedures are presented. The inclusion and exclusion criteria are defined. In addition, the reliability and validity of the selected outcome measures and instrumentation are reported.

Research Design and Methods

This study is a prospective comparison group design with repeated measures. The study was conducted at Stony Brook University's (SBU) Rehabilitation Research and Movement Performance (RRAMP) laboratory in Stony Brook, NY. An FES ergometer (RT300, Restorative Therapies, Inc., Baltimore, MD) and a BTS G-Walk® system, along with BTS G-Studio software (BTG Bioengineering, viale Forlanini 40, 20024 Garbagnate Milanese MI, Italy and 147 Prince Street, Suite 11, Brooklyn, NY), were utilized in this study. Institutional Review Board (IRB) approval for this research was obtained first from Stony Brook University (IRBNetID: 534378-15) on May 29, 2015, and Nova Southeastern University issued an authorization agreement (IRB Registration #: 00000054) on October 2, 2015. Continuing IRB review through Stony Brook University was obtained annually and the project remained active through March 2, 2018.

Recruitment Procedures

PWMS were recruited from various sources including: physician practices, physical therapy practices, support groups, web postings, email, fitness centers, and personal communication. Stony Brook University Medical Center (SBUMC) is a designated MS Comprehensive Care Center and is accredited by the National Multiple Sclerosis Society. See appendix A for a copy of the recruitment flyer and physician letter.

Description of Human Participants

Participants were screened over the phone for eligibility based on inclusion/exclusion criteria (Table 3-1) and Patient Determined Disease Steps (PDDS) criteria (appendix B). Once the met initial eligibility requirements, they participated in an in-person assessment session for further screening.

During the in-person screening session, potential participants were screened for cognitive deficits using the Montreal Cognitive Assessment (MoCA) (appendix C).[110] Potential participants completed a demographic and medical questionnaire (appendix D) to determine if they met the remaining inclusion and exclusion criteria. Once they met the full eligibility criteria, a physical assessment (appendix E) was completed including joint range of motion, the degree of spasticity, sensory function, motor function, and functional mobility.

Table 3-1 Inclusion and Exclusion Criteria

Inclusion Criteria
Medical Diagnosis of MS
At least 18 years of age, inclusive
Patient-determined Disease Steps (PDDS) score between 3.0 and 6.0 inclusive
Ability to attend training sessions 3 times per week for an 8-10 week period
Passing a submaximal exercise tolerance test
Adequate hip range of motion (at least 110 degrees)
Adequate knee range of motion (10-90 degrees)
Exclusion Criteria
Cognitive deficits (score < 22/30 on the Montreal Cognitive Assessment) that would interfere with their ability to sign consent and understand study procedures
History or presence of other neurological pathologies that interfere with movement
Received physical therapy within the 4 weeks prior to the study
History of an acute exacerbation within the 4 weeks prior to the study
Immunosuppressive or steroid therapy within the past 4 weeks prior to the study
Significant spasticity (Modified Ashworth Score ≥ 3 at the quadriceps and hamstring muscles) that interferes with the cycling motion
History of congestive heart failure
Coronary artery disease
Uncontrolled hypertension
History of epilepsy or history of seizures
Cardiac demand pacemaker or implanted defibrillator
Unhealed fractures in the lower extremities
Pressure sores or open wounds on the LEs
Pregnant or trying to conceive

Eligible participants were consented (appendix F: Research Consent Form) in accordance with the Declaration of Helsinki and then randomly assigned to either the FES Cycling group or the Cycling Only group using blocked randomization in order to ensure equal numbers in each group. Group assignment was performed by placing four slips of paper in a box. Two slips said "FES" and the other two said "Cycling." The investigator had participants select a slip of paper from the box after the consent process. Once all 4 slips were selected, they were returned to the box for the next four subjects. A detailed procedure manual for the study is available in appendix G.

Classification of Disability in MS

The EDSS is the most common tool used by neurologists and researchers to classify disease stages in PWMS. The scale ranges from 0 to 10 in .5 unit increments; the higher an individual is on the scale, the greater the level of disability.[53] Those who score from level 1.0 to 4.5 represent individuals with a high degree of ambulatory ability with fewer limitations. Individuals who score from 5.0 to 9.5 represent individuals with a greater loss of ambulatory ability.[111] The categories range from, (0) = *normal neurologic exam*; to (5) = *ambulatory without aid or rest for 200 meters and disability severe enough to impair full daily activities*; to (10) = *death due to MS*.[53] While EDSS is the gold standard for classifying disease stages in PWMS, its ability to measure changes in disability is limited and its responsiveness in measuring change after a therapeutic interventions are poor.[50,112,113] In addition, the EDSS must be administered by a trained neurologist, making it difficult for accurate data to be readily available for research.

Patient-reported outcomes of disability in MS have been used as inclusion criteria in clinical trials as a replacement for the EDSS.[114,115] It has been suggested that such measures can be more cost effective, practical, and convenient than the EDDS.[116] The Patient Determined Disease Steps (PDDS) was developed from the Disability Steps (DS), which was designed to determine disability mainly based on ambulation and motor functioning.[117,118] The DS was then converted into a scale for patient use by the North American Research Committee on MS (NARCOMS) and the PDDS is considered a self-report surrogate of the EDSS.[119] The PDDS was used as part of the inclusion criteria for participant selection for the current study. The PDDS is a nine-level ordinal scale ranging between 0 (normal) and 8 (bedridden). Learmonth et al[116] found a strong correlation

between the EDSS and PDDS in a sample of 96 individuals with MS (p = 0.78, 95% CI = 0.691- 0.850, p = 0.0001). Based on a regression equation of EDSS scores on PDDS scores, the research group was able to determine that a score of 0 (normal) on the PPDS equates to 2.9 on the EDSS scale. The scales do not exactly correspond to each other, but a relationship exists when using the following equation, EDSS score = 2.9 + .63(PDDS).[116] The PDDS and EDSS were also strongly correlated with ambulatory measures such as the 6 Minute Walk (6MWT), Timed 25-Foot Walk (T25FW), Timed Up and Go (TUG), and the 12 item Multiple Sclerosis Walking Scale (MSWS-12), and no significant differences between the correlations for each measure were found.[116] Based on these findings and its clinical utility, the PDDS has adequate criterion and construct validity.[116]

In this study, individuals who rated themselves between 3 (Gait Disability) and 6 (Bilateral Support) on the PDDS were eligible to be included in this study. These criteria were chosen based on the research questions related to walking ability.

Cognitive Screening

Since PWMS can present with cognitive impairments, a screening was performed to assess each participant's capacity to provide informed consent, understand basic instructions, and provide feedback during training sessions. There is no universally accepted screening measure to determine capacity to give informed consent in research studies, but there is a consensus that screening should be related to the risks presented by the research.[120] Although this study presents minimal risk to participants, it was important for participants to have an understanding of the equipment, training, and protocol being utilized.

In order to screen for cognitive deficits, the Montreal Cognitive Assessment (MoCA) was used (permission to use MoCA received from Dr. Ziad Nasredine, via email communication, October 20, 2014). The MoCA was developed to assist physicians in screening for mild cognitive impairment (MCI)[121] and is feasible to use in clinical trials.[122] The MoCA is a 30-point test that can be administered in 10 minutes and contains tasks that assess orientation, short-term memory, visual-spatial ability, attention, concentration, working memory and language.[110,121]

The MoCA is reported to have greater sensitivity and specificity than the widely utilized Mini-Mental State Examination (MMSE) in detecting MCI and a score of 26 was determined to be the cut-off for detecting differences between MCI and Alzheimer's Disease.[121] In PWMS (EDSS = 2.6, SD = 1.87), the MoCA has been compared to another commonly used cognitive measure, the Multiple Sclerosis Neuropyschological Questionnaire (MSNQ), which has two versions, the MSNQ-P and MSNQ-I. The MSNQ-P is filled out by the patient and the MSNQ-I is filled out by an informant, such as a family member or close friend.[123] A significant moderate correlation between the MSNQ-I and the MoCA ($r = -0.390$, $p = 0.012$) was found, but no significant relationship between the MSNQ-P and the MoCA was found ($r = -.300$, $p = 0.06$). The MoCA also demonstrated good construct validity when compared to a combination of cognitive tests that evaluated three cognitive domains: executive/speed of information processing, learning, and delayed recall ($r = 0.37$, $p = 0.03$; $r = 0.69$, $p < 0.001$; $r = 0.636$, $p< 0.001$).[123]

The range on the MoCA for those with mild cognitive deficits ranges from 19 – 25.2 with a SD = 3.1.[110] In this study a cut-off score of 22 or less was used as exclusion criteria. A score of 22 was chosen since it is one standard deviation (SD) above the lower end of

the range of mild cognitive deficits. The PI wanted to ensure that the people participating in this study understood the procedures and protocol.

Baseline Activity Measure

Godin Leisure-Time Exercise Questionnaire (GLTEQ)

The GLTEQ is a short, self-administered questionnaire that asks a person to report the frequency of strenuous, moderate, and mild activity during a typical week.[124] The frequencies are multiplied by metabolic equivalents and then added together to give a total leisure time score. The GLTEQ was administered at the beginning of the study to gather baseline information regarding physical activity levels. The GLTEQ is a valid measure of physical activity in healthy individuals when compared to maximum oxygen uptake testing (VO_2 Max).[124] The GLTEQ form is available in appendix H.

Outcome Measures

Outcome measures were selected based on the International Classification of Functioning, Disability, and Health (ICF) model, recommendations from the APTA Neurology Section's Multiple Sclerosis Outcome Measures Taskforce,[125] clinical expertise, and research goals of the current study (Table 3-2). Members of the taskforce developed specific recommendations for practice environments (entry-level education, research, acute care, inpatient and outpatient) and also rated each outcome on a 4-point ordinal scale (4= highly recommended, the outcome measure has excellent psychometric properties and clinical utility; 3= recommended, the outcome measure has good psychometric properties and good clinical utility; 2= unable to recommend at this time, there is insufficient information to support a recommendation of this outcome measure; 1= not recommended, the outcome measure has poor psychometric properties and/or

poor clinical utility). All measures that were recommended for research were considered if they were rated a 3 or 4.[126]

The chosen battery of outcome measures for this study were: 6 Minute Walk Test (6MWT), Timed 25-Foot Walk (T25W), Timed Up and Go (TUG), 5 Times Sit-to-Stand (5XSST), 12 Item Multiple Sclerosis Walking Scale (MSWS-12), Modified Fatigue Impact Scale (MFIS), Multiple Sclerosis Quality of Life Inventory (MSQOL-54), and Activities-specific Balance Confidence (ABC) Scale. Objective outcome measure procedures for the 6MWT, T25FW, TUG, and 5XSST can be viewed in appendix G. Self-report outcome measures are available in appendix I-L.

Selected outcome measures were collected at the following intervals:

- baseline - within one-week prior to the first training session;
- mid-point of training - before 13th training session;
- post-training - between 1-3 days after the 24th training session, and
- follow-up - one-month after the last training session.

Physical tests were administered in the following order for each participant: 6MWT, T25W, TUG, and 5XSST. Participants were provided at least a five-minute rest period between all physical tests. Safety precautions during testing included: a quiet area free of distractions, gait belt, guarding, and assistance as needed. In order to measure both temporal and spatiotemporal gait parameters, the BTS G-Walk® (Table 3-3; Figure 3-1) was utilized to collect gait data during the 6MWT, TUG, and T25FW. The G-Studio software automatically generated spatiotemporal parameters after each trial.

Reliability and Validity of Selected Measures

Clinical Measures

For all physical measures, a participant's regular footwear was worn during data collected and participants were instructed to wear the same footwear for each testing session. Each participant wore a gait belt and the investigator was nearby, but behind the participant so that their speed was not influenced by the investigator. If an assistive device was utilized by a participant in their daily life, they were instructed to use it during all physical measures except the 5XSST. Each participant received scripted instructions each time they completed these tests.

6 Minute Walk (6MWT)

The 6MWT measures a person's self-paced walking distance over a 6 minute period and is a valid and reliable measure of walking performance in PWMS.[127–129] The 6MWT was found to have excellent test-retest reliability (ICC = 0.96, 95% CI 0.87- 0.99) over a one-week interval in PWMS (EDSS 2.0 – 6.5).[130] Pilutti et al[114] also found there to be a significant difference between the 6MWT performance in PWMS with mild vs. moderate to severe disability (mild= 530.7m, range 292.6 - 782.1m, moderate to severe= 349.8m, range 51.5 – 605.3m, $p < 0.0001$). It was also found that PWMS (EDSS 2.0 - 6.4, median 4.0) classified as fallers demonstrated a significant difference in the their 6MWT distance compared to a group of non-fallers (fallers = 1288 feet, non-fallers = 1533 feet, $t = 2.2$, $p = 0.02$).[64]

Table 3-2 Outcome measures

Outcome Measure	Collection of Data
12 Item Multiple Sclerosis Walking Scale (MSWS-12)[A]	• Baseline • Post-training • 1 month after training
Modified Fatigue Impact Scale (MFIS)[B, A, P]	• Baseline • Post-training • 1 month after training
Multiple Sclerosis Quality of Life Inventory (MSQOL-54)[A, P]	• Baseline • Post-training • 1 month after training
Activities-specific Balance Confidence (ABC) Scale[P]	• Baseline • Post-training • 1 month after training
6 Minute Walk (6MWT)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Timed 25-Foot Walk (T25FW)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Timed Up and Go (TUG)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Five Times Sit-to-Stand (5XSST)[A]	• Baseline • Mid-point • Post-training • 1 month after training
Spatiotemporal Outcomes[A] **6MWT and Timed 25-Foot Walk (T25FW)[A]** **Stride length, Step Symmetry & Double-limb Support [A]** **Temporal Outcomes** **TUG [A]** **Sit to Stand and Stand to Sit Phase Duration** **Mid-turning and End-turning Phase Duration**	• Baseline • Mid-point • Post-training • 1 month after training

ICF Model Domain: B, Body Structures & Function; A, Activity; P, Participation

Table 3-3 BTS G-Walk® Technical Specifications

Dimensions	70 X 40 X 18 mm
Weight	37 grams
Sensors typologies	Triaxial accelerometer 16 bit/axes with multiple sensitivity (±2, ±4, ±8, ±16 g) Triaxial magnetometer, 13 bit (±1200 uT) Triaxial gyroscope, 16 bit/axes, with multiple sensitivity (±250, ±500, ±1000, ±2000 °/s)
Battery	Rechargeable via USB 8 hours of autonomy
Frequency	Accelerometer: from 4 to 1000 Hz Gyroscope: from 4 to 8000 Hz Magnetometer: up to 100 H
Working	Real-time/batch

Figure 3-1 BTS G-Walk® Sensor and Ergonomic Belt

Cadence and stride length also explain differences in 6MWT performance in people with mild, moderate, and severe MS when controlling for age ($F\{2,299\} = 38.17$, $p<0.001$, partial $-\eta^2 = 0.20$; $F\{2,299\} = 44.30$, $p< 0.001$, partial $-\eta^2 = 0.23$, respectively), but there was no significant difference in cadence between a control group and people with mild MS ($p = 0.06$).[114] Using a regression analysis, these researchers also demonstrated that cadence and stride length explained the difference in the 6MWT between PWMS and controls.[114]

In this study, the testing area was a rectangular walkway (40ft x 12ft), clear of obstructions and foot traffic. The 6MWT instructions were standardized and adapted from Goldman, Marrie, and Cohen.[129] Participants were instructed to walk as far and as fast as possible for 6 minutes while being mindful of their exertion. All participants completed the 6MWT without requiring seated rest periods. One participant needed to take brief standing pauses during the test. When participants completed the 6 minutes, the spot where they were instructed to stop was marked and distance was recorded in feet and then converted to meters. Participants wore the BTS G-Walk® during the 6MWT to collect spatiotemporal data since these parameters may further explain improvements in performance in PWMS.

Timed 25-Foot Walk (T25FW)

Walking speed is a commonly used measure in clinical practice and has been cited in the literature as the "sixth vital sign."[131] Gait speed was measured using the T25FW and participants were instructed to walk at a "fast but safe speed" consistent with a protocol suggested by Gijbels et al[132] and Bethoux and Bennett.[133] This measure was chosen due to its clinical utility, ease of administration and common use as part of the MSFC.[134]

The minimally important clinical difference (MICD) has also been established for the T25W and will allow for post-test comparisons regarding gait speed.[135–137] For individuals with greater disability, a ≥ 20% change in the T25FW correlates with clinically meaningful change when compared to other measures such as the MSWS-12[135] and EDSS.[148] The T25FW has a floor effect and is less sensitive in detecting clinical change in those with mild disability.[133]

Goldman et al[136] examined changes in the T25FW in relation to changes in life roles. A T25FW of 6.0 to 7.99 seconds is related to a change in occupation, unemployment, walking with a device, and/or the need for some help with instrumental activities of daily living (IADL). Walking speeds greater than or equal to 8 seconds are related to the need to use a walker and inability to perform IADLs.[136] The T25FW failed to detect differences in gait speed in individuals who are classified as fallers vs. non-fallers ($p = 0.06$).[114] This may be due to several factors, including the contribution of fatigue to falls in PWMS. This provides justification as to why the 6MWT may be a better measure to detect fall risk in PWMS.[114]

In this study, individuals walked a straight 25-foot distance with an added distance of 10 feet at the beginning and end to allow for acceleration and deceleration. Two trials were collected and averaged. Participants were instructed to walk as quickly and as safely as possible.

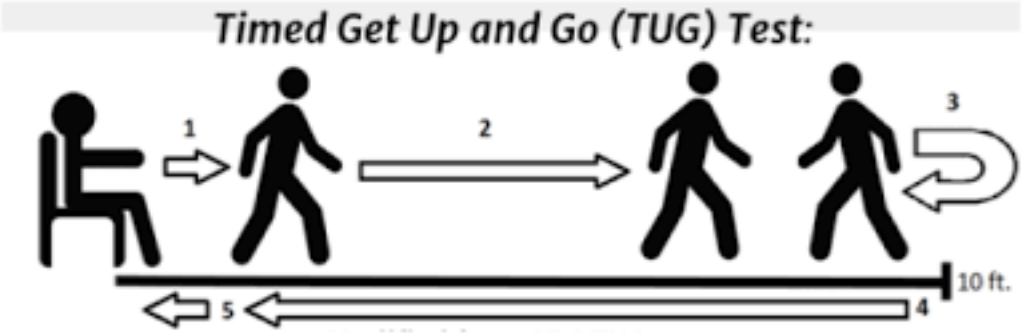
Timed Up and Go (TUG)

The TUG is a simple and widely used performance-based measure that is significantly related to fall risk in healthy older adults and it is commonly used in research and clinical settings.[140] The TUG measures the time it takes in seconds to stand up, walk 3 meters, turn around and walk back to a chair and sit down. Higher times reflect a greater risk of falls. The TUG is validated for use in PWMS[127,128] and demonstrates good test-retest reliability (EDSS ≤ 4.0, ICC = 0.84, CI = 0.66- .93; EDSS > 4.0, r = 0.88, CI = 0.76 - 0.95).[141] In PWMS with an EDSS between 4.0 and 6.0, researchers have established a strong correlation between the TUG and the Functional Ambulatory Profile (FAP) ($r= -0.88$, $p< 0.05$), gait velocity ($r= -0.90$, $p <0.05$), double support time ($r = 0.81$, $p<0.05$),

single-support time (r= -0.86, p< 0.05), and base of support (r = 0.48, p< 0.05).[65] In addition, PWMS (EDSS 2.0 -6.5, median 4.0) classified as fallers demonstrated higher TUG times compared to a group of non-fallers and scores were significantly different between these two groups (t = - 1.7, p = 0.04).[64] On average, TUG scores for fallers were 9.7 seconds and for non-fallers 7.8 seconds.[64]

In this study, a standard height chair (seat to floor height = 18 ½ inches) was placed at the beginning of the 3-meter (approx. 10 feet) walkway and the participant turned around a cone (Figure 3-2). Data on phase duration for sit to stand, stand to sit, mid-turning, and end-turning were collected using the BTS G-Walk®.

Figure 3-2 Timed up and Go



Five Times Sit-to-Stand (5XSST)

The 5XSST is a timed test that measures how long it takes for an individual to repeatedly transition from sitting to standing. Evidence supports that sit-to-stand tests are appropriate and time-efficient tests to use in the clinical setting to assess LE strength.[142,143] A strong relationship between a 10 times sit-to-stand test and knee extensor and flexor strength was found in 139 healthy individuals ages 20-62.[142]

Currently, there is no data available that demonstrates the reliability or validity of the 5XSST in PWMS. The 5XSST has been found to be a valid and reliable measure of fall risk in people with PD[144] and the older adult population.[145,146]

In this study, the same chair utilized for the TUG measurements was also used for the 5XSST. Participants received scripted instructions to stand up and sit down as quickly as possible 5 times, keeping their arms folded across their chest. If the participant used arm rests to safely sit and stand, they were permitted to do so, and when the test was repeated at the various time points, participants were tested in the same manner. One trial of the 5XSST was performed and the timer was started when the participant's buttocks left the seat and stopped when the participant stood the 5th time.

BTS G-Walk®

The BTS G-Walk® wireless inertial sensor was secured on the elastic belt in a pouch and placed on the L5 vertebrae to collect gait data during the 6MWT, T25FW, and TUG. Evidence supports that body-worn motion sensors provide additional information about gait and balance that standard timed walking tests do not detect.[147] The BTS G-Walk® has been validated by BTS Bioengineering by comparing key gait parameters (stance phase, swing phase, double support phase, and gait cycle duration) to the BTS GAITLAB (standard motion analysis) in 30 healthy adults, 25-50 years old and found the BTS G-Walk® to be accurate with a deviation of 2.28%.[148]

Self-Report Measures

For all self-report measures, participants were oriented to the measure and given the opportunity to ask questions. Participants completed the measures at home and

brought them in the next training session. The measures were reviewed to ensure they were filled out in their entirety.

12 Item Multiple Sclerosis Walking Scale (MSWS-12)

The MSWS-12 is a 12-item self-report questionnaire[149] that takes approximately 10 minutes to complete and reflects a persons' perception of the impact that MS has on walking ability during the past 2 weeks. Each of the items scored ranges from 1 to 5, in which higher scores indicate a greater impact of MS on their walking. The scores were summed and then transformed to a 0 -100 scale by subtracting 12 from the total, dividing by 48, and then multiplying by 100.

The MSWS-12 has strong psychometric properties, including good internal consistency (Cronbach's alpha = 0.97) and test-retest reliability (ICC = 0.94).[150] Concurrent validity has been demonstrated by comparing the MSWS-12 to other commonly used self-reported measures and physical mobility measures. Using Cohen's interpretation of correlation (0.10 = small, 0.30 = medium, 0.50 = large),[151] the MSWS-12 demonstrates a medium to large correlation with EDSS scores (EDSS 1.0 - 4.5, r = 0.71, EDSS 5.0 – 8.0, r = 0.33, EDSS 1.0 – 8.0, r = 0.80, p = 0.0001), large inverse correlations to movement measured by an accelerometer over a 7- day period (EDSS 1.0 - 4.5, r = -0.51, EDSS 5.0 - 8.0, r = -0.48, EDSS 1.0 – 8.0, r = -0.64, p = 0.0001), and large correlations with the physical impact subscale of the Multiple Sclerosis Impact Scale (MSIS) (EDSS 1.0 - 4.5, r = 0.74, EDSS 5.0 – 8.0, r = 0.75, EDSS 1.0 – 8.0 , r = 0.77, p = 0.0001).[150,152] In addition, in individuals with RRMS (EDSS not reported), the MSWS-12 was highly correlated with the oxygen costs of "comfortable walking" during a 6MWT (r = 0.64, p = 0.001).[153] In a study measuring self-reported health status at admission and discharge, the MSWS-12

demonstrated strong responsiveness (effect size = 0.89) to receiving inpatient rehabilitation in a sample of 43 PWMS (mean EDSS = 7.2).[154] Responsiveness, minimal clinically important difference (MCID), or minimal detectable change (MDC) of the MSWS-12 to exercise training trials have yet to be established at the time of this review.

Modified Fatigue Impact Scale (MFIS)

The MFIS (a modification of the Fatigue Impact Scale (FIS) that was introduced in 1994),[155] is a component of the Multiple Sclerosis Quality of Life Inventory (MSQLI). The original FIS was constructed based on interviews with people living with MS and how fatigue impacted their lives.[155] The MFIS is a 21 item self-report questionnaire that takes 5-10 minutes to complete. It uses a 5-point likert scale to rate the patient's perception of how MS-related fatigue affects an individual's life on an everyday basis. It contains three subscales that include: cognitive, physical, and psychosocial dimensions. Scores on the subscales can be analyzed individually or as a summed score to give an overall fatigue score. Higher scores indicate a greater impact of fatigue.

Researchers demonstrated that the psychometric properties of the MFIS include low floor and ceiling effects, (1.1% and 0.7%, respectively)[156] and good internal consistency (Cronbach's alpha = 0.96).[116] In a study conducted in four European countries, the MFIS demonstrated good test-retest reliability (ICC range = 0.84 - 0.93, 99% CI),[117] which is similar to the test-retest reliability demonstrated in other studies.[158] The MFIS also demonstrates good construct validity when compared to the Fatigue Severity Scale (r = 0.47).[156]

In a study by Rampello et al[12] the MFIS scores did not significantly change after either aerobic training or standard neurological rehabilitation in a sample of 19 subjects with mild to moderate disability. A 12-week supported treadmill training study also failed to demonstrate any significant changes in the MFIS,[159] so it appears the MFIS may lack the ability to measure responsiveness[158] to change in fatigue over time. Although other fatigue scales exist that demonstrate similar properties,[156] the MFIS was chosen because it represents a broader range of fatigue than other scales and takes into account the previous 4 weeks of fatigue, versus other scales, such as the Fatigue Severity Scale (FSS), which only asks individuals to evaluate their fatigue from the previous week. Since fatigue can vary greatly in PWMS, capturing a 4-week overview may be a more accurate representation of fatigue.

Multiple Sclerosis Quality of Life Inventory (MSQOL-54)

The MSQOL-54 is a multidimensional self-report quality of life questionnaire that takes 15-30 minutes to complete (permission to use MSQOL-54 received from Barbara Vickry, MD, MPD, via email communication, March 21, 2014).[160] This questionnaire measures health-related quality of life using both generic and disease-specific measures and was constructed by experts in the field.[160] This measure was chosen since it is more comprehensive than other MS disease-specific quality of life scales and is recommended for use amongst a group of multidisciplinary international experts.[161]

Researchers created this inventory by combining disease-specific questions that include impairments such as fatigue and cognition with a generic health-related quality of life scale (short-form 36-health questionnaire). There is no overall score for the MSQOL-54 since it contains 12 subscales, two summary scores, and two single-item measures.

The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are satisfaction with sexual function and change in health.

The psychometric properties of the MSQOL-54 subscales show good internal consistency (Cronbach's alpha = 0.75 - 0.96) and good test-retest reliability with ICCs ranging from 0.69 to 0.96.[160] In addition, the MSQOL-54 demonstrates moderate responsiveness on both the physical and mental summary scales (standard responsiveness mean for physical scale = 0.71 and mental scale = 0.57).[162] In an aerobic training study by Rampello et al[12] the researchers found significant changes in three of the MSQOL-54 scale scores (emotional well-being, energy, and health distress).

Activities-specific Balance Confidence (ABC) Scale

The ABC measures an individual's perceived level of balance confidence when performing 16 activities of daily living. Each item is rated on a scale of 0% to 100% ("no confidence" to "complete confidence") and then a mean score is calculated.[163] This scale was originally designed to be used in community-dwelling elders,[163] but has been subsequently used in neurological populations.

The ABC has been utilized and studied in PWMS, and significant differences in scoring balance confidence have been found when PWMS were compared to age-matched controls.[147] In PWMS, the ABC was found to have good clinical utility since it can be used as a predictor of falls.[127] When comparing fallers vs. non-fallers, the ABC demonstrated significant differences in scores with a score > 40 classifying an individual as a faller with

a sensitivity of 65% and specificity of 77%.[127] Dibble et al[164] found significant differences between fallers and non-fallers on the ABC, Dynamic Gait Index (DGI), and Berg Balance Scale (BBS) ($p < 0.05$ for all tests). When compared to other commonly used clinical balance measures, such as the BBS, DGI, and TUG, the ABC demonstrated good validity ($r = -0.32$, $r = -0.39$, $r = 0.35$, $p < 0.0001$ for all tests).[127] In PWMS, the ABC has also been found to have excellent test-retest reliability (ICC = 0.92, CI = 0.80 - 0.97) and no ceiling effect in PWMS.[165]

Submaximal Exercise Tolerance Testing

The assessment for exercise tolerance was designed in coordination with the American College of Sports Medicine (ACSM) guidelines.[166,167] ACSM recommends that before beginning an exercise regimen, professionals employ two or more techniques to measure relative intensity.[166] ACSM suggests using submaximal testing[166] as a practical approach to testing since most physical therapists do not have the necessary equipment for metabolic testing. Heart rate (HR), blood pressure (BP), and rating of perceived exertion (RPE) can be used to measure to measure relative intensity during a graded exercise test.[166] In this study, a submaximal clinical exercise tolerance test (SXTT) was performed on the LE ergometer used in the intervention since recommendations support that it is best to do exercise testing on the equipment used for training.[168]

This study followed the ACSM recommendations for performing exercise testing for persons with MS.[169] These recommendations include:

- testing in the morning, if this is the optimal time for the participant
- beginning with a warm-up of unloaded pedaling

- using a fan for cooling as needed
- using a continuous or discontinuous protocol of 3 to 5 minute stages with an increase of work rate of approximately 12 to 25 Watts (W) per stage
- monitoring heart rate and blood pressure
- using the RPE scale to estimate stress level (Appendix J)[166]

In this study, the SXTT was conducted on the RT300 LE ergometer which was the same equipment being utilized during training (Figure 3-3; Table 3-4) (RT300, Restorative Therapies Inc., Baltimore, Maryland, USA). Participants were asked to cycle at a target speed of at least 45 rpm, or the maximal speed they were are able to sustain, while the investigator systematically increased resistance. The participant began with an interval of unloaded cycling followed by an increase in resistance every 3 minutes. Resistance was increased 3 Newton-meters (Nm) per stage, which is approximately 14 Watts per stage.[16,169] The SXTT was discontinued when the participant reached self-reported fatigue, if their vital signs fell outside a safe range, or if they could not maintain 45 rpm speed. Maximal workload was defined as the last interval a participant can cycle at least one-minute. HR, pulse oxygen (SPO_2) and BP were measured at baseline, and then recorded during the last minute of each testing intervals.[167] In addition, the RPE scale was introduced to participants and scores were reported recorded during the last 15 seconds of each interval (see appendix N).

During the SXTT, ACSM's guidelines for discontinuing testing were followed and included:[16,167]

- self-reported fatigue- participant expressed they can no longer pedal due to fatigue
- reaching 70% heart rate reserve, which is 85% of age-predicted HR_{max}, (HR_{max} = 220 – age x .85)
- failing to conform to exercise protocol, which for this study was defined as falling 10 rpm below the target rpm speed of 45 for greater than 10 seconds.
- hypotensive responses- systolic BP drops ≥ 10 mmHg from baseline[167]
- hypertensive responses- systolic BP increases to > 250 mmHg and/or a diastolic BP increase of > 115mmHg[167]
- symptom exacerbation,[168,169] including headache, change in vision, numbness, sudden paralysis, dizziness, and vertigo
- chest pain, shortness of breath, wheezing, and leg cramps[167]

Figure 3-3 RT300 LE Ergometer (Restorative Therapies, Reprinted with permission)

Table 3-4 RT 300 and Sage Controller Technical Specifications

Length	31.5" or 80 cm
Width	19.3" or 49 cm
Height	36.2" – 40.6" or 92 – 103 cm
Length of leg pedal	4.3" or 11 cm
Speed Range	20 – 55 rev/min (+/- 2 rev/min)
Torque range	1 – 22Nm (+/- 1Nm)
Controller Display/Interface	Touch-sensitive LCD
Communications	Wireless or Ethernet
Operating System	Windows Mobile

Training Protocols

Participants trained for 45 minutes, three times- per-week, for approximately 8-weeks using the RT300. Basic demographic information (age, weight, and diagnosis) was entered into Restorative Therapies Internet (RTI) Data Link and a random ID number was generated along with a four-digit pin number. The participant number was used as the participant ID number on all paperwork associated with the study.

Participants were positioned in the training chair (Figure 3-4; Table 3-5) and their LE's were placed on the bike pedals and secured using strapping according to the manufacture's recommendations. The bike and chair were positioned to maintain approximately 5-15 degrees of knee flexion when in the fully extended position of cycling. The height of the ergometer was adjusted so that the rear of the participant's thigh did not press into the seat cushion during cycling. In order to optimize positioning and cycling angles, when necessary, adjustments to seat height and depth were made utilizing cushions. Each participant's set-up was documented and used every training session.

Figure 3-4 TUG, 5XSST and Training Chair

Table 3-5 Chair Specifications

Manufacturer	OFM™ Anti-Bacterial Vinyl Padded Guest/Reception Chair With Arms
Model	811588014224
Arm Type	Fixed
Seat Dimensions	19 1/2" X 19 1/4"
Seat to Floor Height	18 ½ inches
Weight Capacity	Up to 250 pounds

FES Cycling Protocol

In the FES Cycling group, the stimulated muscles were standardized and included the gluteals, hamstrings, quadriceps, anterior tibialis, and gastrocnemius. At the beginning of every session, the skin was cleaned with alcohol and dried prior to electrode placement. Each participant had their own set of electrodes that were labeled with their participant number and stored at the research lab. Electrodes were placed according to the guidelines outlined and participant morphology (Table 3-6; Figure 3-5). Before and after each training session, skin was inspected for erythema, breakdown and/or irritation. Expiration dates on the electrodes were checked prior to usage. The manufacturer of the electrodes recommends that each electrode be used for a maximum of 10-15 sessions. If

an electrode no longer adhered appropriately to the skin, it was discarded, and a new electrode was utilized. In order to track usage, each participant's package of electrodes was labeled with the date of each session. Further detail regarding electrode placement and set-up can be reviewed in appendix G.

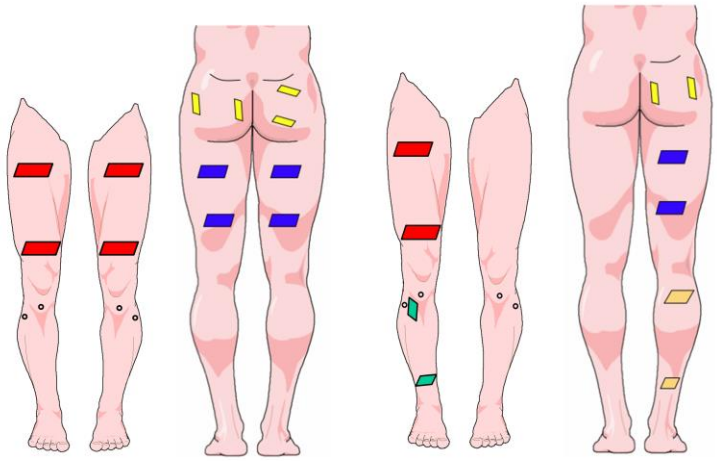
After all objective outcome measures were obtained, initial stimulation settings were set during the baseline testing session prior to the training period. Standardized instructions were read to each participant prior to set-up and can be reviewed in appendix G.

Table 3-6 Electrode sizing and placement

Muscle	Electrode Size	Location of placement
Quadriceps	3" X 4"	One electrode was placed a hand width above the knee centered on the belly of the quad and the second electrode was placed at least a hand width above the first electrode. For participants with a longer thigh length, it was placed higher on the quadriceps belly.
Hamstrings	3" X 4"	Electrodes were placed in line with the quadriceps electrodes, but on the back of the thigh and were centered in the middle of the hamstrings.
Gluteals	2" X 3.5"	One electrode was placed vertically with the top of the electrode parallel to the top gluteal cleft and the second electrode two-finger widths lateral to the first electrode.
Anterior Tibialis	2" X 3.5"	One electrode was placed proximally on the muscle belly and the second electrode was placed distally about 2/3 way down the shin.
Gastrocnemius	2" X 3.5	One electrode was placed horizontally across the calf, just below the knee and the second electrode was placed just distal to the gastrocnemius belly.

*The electrode sizes above were used as guidelines and individual adjustments were made based participant morphology.

Figure 3-5 LE Electrode Placement Guidelines (Restorative Therapies, Reprinted with permission)



Stimulation frequency for all participants was set at 43.5Hz for all muscle groups and was not changed throughout the study. During this baseline session, participants cycled against their starting resistance obtained on the SXXT (60% of the maximal resistance achieved during the SXTT[168]). All muscle groups were stimulated with a starting pulse width of 250μsec. Amplitude ramped up at 1% per second and the participant was instructed to tell the investigator to hold the stimulation when they felt any of their muscles reach a point where the stimulation was uncomfortable. The investigator then adjusted each muscle group individually to its maximal tolerable stimulation while the participant continued to cycle. Adjustments in amplitude were increased in increments of 1mA until a participant achieved a strong muscle contraction or reached his or her tolerance to stimulation. If a participant's tolerance to stimulation was reached before a detectable contraction was palpated, pulse width was decreased by 10μsec increments and then amplitude was increased by 1mA increments until a strong,

but tolerable muscle contraction was achieved. The maximum level of stimulation was set at the value that has been determined to create the strongest tolerable motor response. If a participant was still unable to achieve a strong muscle contraction due to discomfort, the highest stimulation parameters they reached were utilized. Parameters were then adjusted during training sessions as participants accommodated to the stimulation. All initial settings were automatically saved in the RTI Data Link database.

The participant's stimulation levels from baseline session were used as starting parameters for the first training session. If, during training sessions, the participant was able to tolerate more stimulation in any individual muscle group, amplitude was increased in 1mA increments. Participants started each session using the stimulation parameters from their previous session.

Participants experienced a 2-minute warm-up period in which the ergometer's motor provided passive in which the motor moved the participants' legs. This allowed for the participant to work out any spasms or stiffness they were experiencing. The ergometer then transitioned into "active mode" in which the electrical stimulation slowly ramped up to allow the individual to accommodate to the stimulation. During this period, the participant received stimulation while also using their own muscle power against a set resistance while working to maintain a set target speed of at least 45 rpm.

Participants were encouraged to cycle for at least 45 minutes using an interval training protocol (5 minutes of active cycling with stimulation, followed by 1 minute of passive cycling without stimulation). This 5:1 ratio was repeated 7 times during each session. At the end of the session, participants received a 1-minute cool-down of passive cycling with no stimulation.

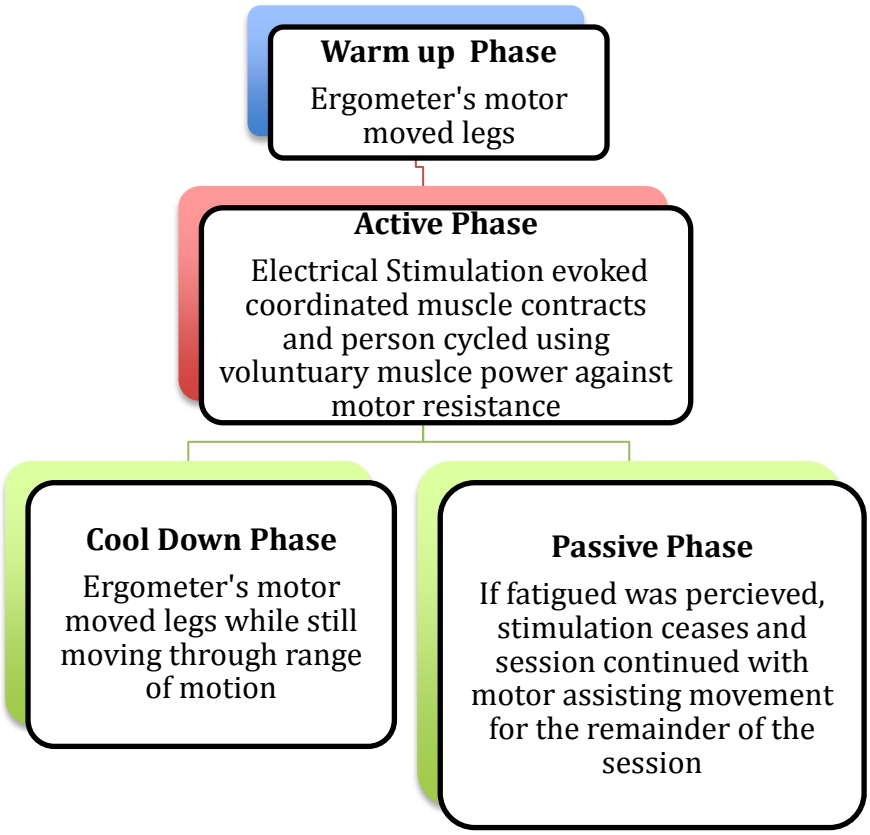
When using FES cycling with other patient populations (e.g. complete SCI) who need stimulation and/or motor support, the ergometer can be set to assist with cycling when they fall below a set control speed. Since all individuals in this study had volitional control to cycle at or above the control speed of 45 rpm, stimulation minimums/maximums were set to the same level to ensure stimulation remained on during the 5-minute stimulation period no matter how fast the participant cycled. Although the ergometer can provide 'motor support,' no participants in this study required assistance from the motor to maintain the minimum control speed of 45 rpm.

If at any time during training a participant reported fatigue and needed to discontinue cycling, stimulation was discontinued, and the participant was permitted to finish the rest of their session in passive mode with the motor fully assisting their movement (Figure 3-6) or restart cycling after a rest period of less than 5-minutes. Only one participant needed to stop one training session due to fatigue.

All participants were able to cycle the full 45 minutes during their first training session using the 5:1 protocol. Resistance was increased after a minimum of 3 sessions, by 5% increments, using a standardized progression protocol. The decision to increase resistance was based on stability of performance (i.e. PRE report, mileage) and investigator expertise. After an increase occurred, the investigator monitored mileage each session. Increases in resistance occurred only when the participant was able to cycle approximately the same mileage as their previous session or if the participant expressed they can tolerate an increase in resistance. Workload was progressively increased during the 24 session training period to a maximum of 80% of the starting

workload.[168] Standardized instructions were read to the participant prior to first training session and can be viewed in appendix G.

Figure 3-6 Therapy Session Progression



Cycling Only Protocol

Participants in this training group were positioned on the RT300 in the same manner as those in the FES training group, but they did not receive electrical stimulation nor wear stimulation pads; the RT300 was used as an ergometer only. Adjustments in resistance were made using the progression protocol described for the FES Cycling group. Standardized instructions were read to each participant prior to set-up and can be reviewed in appendix G.

RT300 Features

Participants in both groups received real-time visual feedback from the screen on the ergometer (Figure 3-7) and summative feedback after their training session. They received information regarding distance traveled, right to left cycling symmetry, power output, heart rate, and SPO_2 and were told not to focus on any one particular outcome.

The RT300 has several features that were utilized during this study. One feature was the "control speed offset." If a participant's cycling speed fell below the target speed by a pre-set revolution per minute (rpm), the ergometer's motor was set to take over for the remainder of the session and assist the participant. The control speed offset was set at -10 rpm for all participants. The target speed for all participants was 45 rpm and if a participant's speed fell below 35 rpm the ergometer's motor took over and the cycle would finish the session in passive mode. This feature was not utilized by any of the participants.

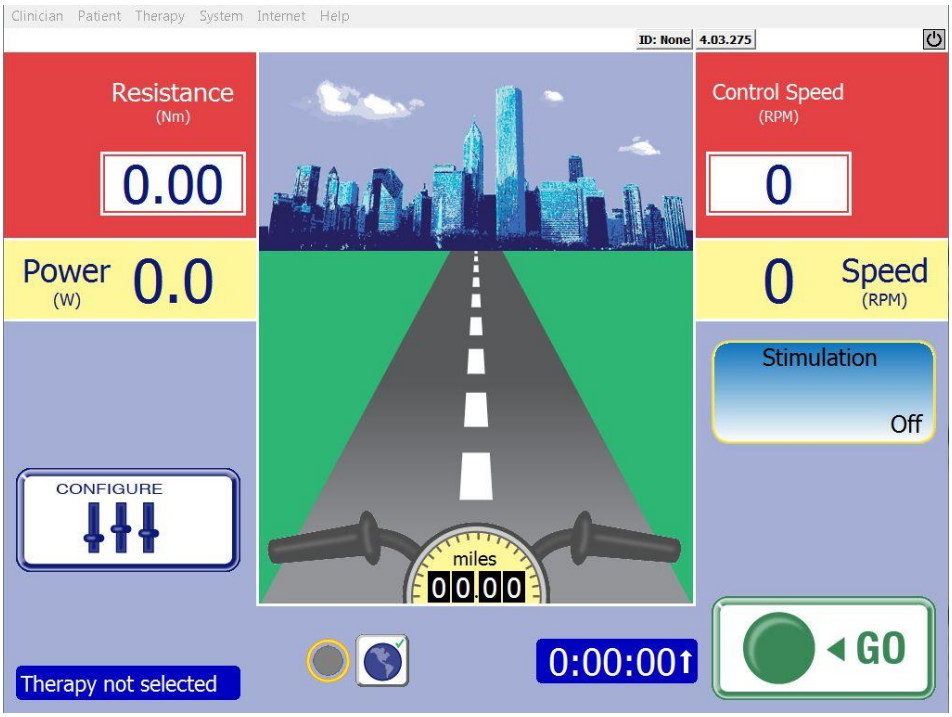
The SAGE stimulator also monitored electrode adherence, so if an electrode fell off during cycling, the ergometer paused and ceased stimulation. An error message was then displayed on the screen indicating which electrode(s) needed to be checked. Once the electrode was secured, the session continued. This occurred infrequently and did not impact training sessions.

All participants were continuously monitored by a wireless HR and pulse oximeter with individually set parameters. Each participant's maximum heart rate was set at 85% of their age-adjusted max HR (220-age x .85). If a participant's HR went above maximum, the ergometer paused, and the participant was given a short rest until their HR returned to their target heart rate range. The minimum heart rate was set at 5 bpm below the

participant's resting baseline to allow for normal HR variability that can occur from day-to-day. The minimum SPO_2 was set at 88% for all participants and there no instances when this parameter fell below 88% during a session.

Each participant's target HR was also calculated (65% of their age-adjusted max HR) and they were encouraged to keep their HR within a target HR range (65% to 85% of their age-adjusted max HR).

Figure 3-7 RT300 Training Screen (Restorative Therapies. Reprinted with permission)



Scheduling of Training Sessions

Schedules were developed to assure the proper timing for training and testing sessions. At least one day of rest was scheduled between training sessions. Participants committed to completing 3 sessions within a 7-day period. Make-up sessions were scheduled as needed on weekends, but the training period was not permitted to extend

beyond a 10-week period. All participants completed their training within the 8 -10 week period. The PI was responsible for scheduling the research space and equipment necessary throughout the study.

Data Safety Monitoring and Participant Confidentiality

Paper records for this study are stored in a file cabinet in a locked closet in the research lab and will be maintained for 5 years after completion of the study. Participant numbers were assigned to each participant from RTI Data Link and were used on all forms associated with the participant. Personal information, including participant number, phone numbers, and email addresses were available only to the PI for the purpose of scheduling on a password protected laptop.

The cycling parameters for each participant were stored under the individual's participant identification number. Data from each training session was automatically saved in each participant's electronic file in RTI Data Link. The RTI Data Link and RT300 are password protected and HIPAA compliant and all participant information was de-identified.

Data Analysis

Data was entered into spreadsheets by the PI and an undergraduate research assistant and were checked for errors.

Descriptive statistics were performed to determine the measures of central tendency. Ordinal baseline demographic data were compared across treatment groups to assess the adequacy of randomization using the Mann-Whitney *U* for ordinal data (PPDS, GLTQ, MoCA, MSWS-12, MSQOL, ABC, MFIS) and independent t-tests for continuous data (age, years since diagnosis, 6MWT, T25FW, TUG, 5XSST).

Descriptive, parametric, and non-parametric statistics were performed using the statistical software program SigmaPlot®, V 12.5, San Jose, CA. To analyze the cycling outcomes for mileage and power output within each group, parametric methods were utilized since the data was continuous, therefore a paired t-test and independent t-test were used accordingly. Between groups comparisons were made using a Two-Way Analysis of Variance (ANOVA).

To analyze the effect of the interventions, a Repeated Measure Analysis of Variance (repeated measure ANOVA) was chosen because since the is no nonparametric test for two-group designs with more than two repeated measures. Between and within group comparisons for each time period and standard error were calculated using a linear mixed-effect model in SAS V9.4 (the SAS Institute, Cary, NC). There were some data points missing at random due to instrumentation errors with the BTS G-Walk® and the mixed-effect model provides flexibility to handle these issues.[170] Missing data included BTS G-Walk,® data at: baseline for the TUG for one FES group participant (FES01), mid-point 6MWT data for two Cycling Only participants (Cycling 01 and 02), and post-training TUG data for one Cycling Only participant (Cycling 04). Cnaan, Laird and Slasor[170] state, "If the missingness is unrelated to outcome, then the maximum likelihood estimates are valid and fully efficient." In addition, the mixed model is a flexible approach and handles uneven spacing of repeated measures and can be generalized to non-normal outcomes. These model uses both fixed effects (treatment levels) and random effects (subjects) to calculate between and within group differences.[171]

Effect size (Cohen's *d*) was also calculated for cycling and clinical outcome measures (6MWT, T25FW, TUG, 5XSST) to examine the magnitude of differences in

outcomes within groups during the training period. A greater effect size indicates a larger difference between groups. An effect size of 0.2 to 0.5 was considered small, an effect size of 0.5 to 0.8 was considered medium, and an effect size above 0.8 was considered large.[151]

This sample size for this study was determined based on intention to complete a clinical pilot study to investigate methodology, clinical outcomes, and tolerance to cycling in PWMS. Data and information collected from this research will be used to conduct a power analysis for a larger scale study.

Resources

The PI performed all data collection at the Rehabilitation Research and Movement Performance (RRAMP) laboratory at Stony Brook University (SBU), in Stony Brook, NY. This research laboratory was equipped with an RT300 ergometer and a BTS G-Walk® system along with BTS G-Studio software. The PI purchased an armchair, water for participants, and office supplies. Restorative Therapies, Inc. provided the electrodes.

The PI was present during all training sessions and performed all outcome measure testing. Since the PI served at the clinician supervising the intervention and data collection, there was no blinding in this study.

The PI was awarded two grants, the New York Physical Therapy Association (NYPTA) Arthur J. Nelson Research Designated Fund ($5,000) and Lee Silverman Voice Training (LVST) Global Small Student Grant Funding ($1,500). The NYPTA grant supported subject honorariums and conference travel, and the LSVT grant provided support for a laptop purchase and statistical consulting from a biostatistician.

Chapter 4

Introduction

This chapter is a narrative of the results of this study along with tables and figures that highlight differences between and within the FES and Cycling Only groups on clinical and self-report measures. Supplemental tables can be found in the appendix and are referenced in the body of the discussion.

Results

Of the 36 PWMS screened for eligibility, 15 met the inclusion criteria and were enrolled in the study. Eight subjects were randomly assigned to the FES Cycling group and seven to the Cycling Only group. All participants met the inclusion/exclusion criteria. One participant in the FES cycling group withdrew after the second session due to developing neck pain and did not continue in the study. Fourteen participants (7 FES Cycling Group, 7 Cycling Only Group) completed training and were included in the analysis. The flow diagram of enrollment in the study based on the Consolidated Standards of Reporting Trials (CONSORT) is reported in Figure 4-1.

Participant Characteristics

Baseline demographics for the overall sample, FES group, and Cycling Only group are presented in Table 4-1. Mann-Whitney U and Independent t tests demonstrated that the baseline characteristics between groups were similar for disease severity, activity levels, cognition, length of time since MS diagnosis ($p > 0.05$). However, there was a significant difference in age between groups with the FES Cycling group being an average of 12 years older than the Cycling Only group ($t_{12} = 2.17$, $p = 0.018$). The FES Cycling

group also had a higher rate of assistive device use for mobility.

Figure 4-1 CONSORT flow diagram of enrollment

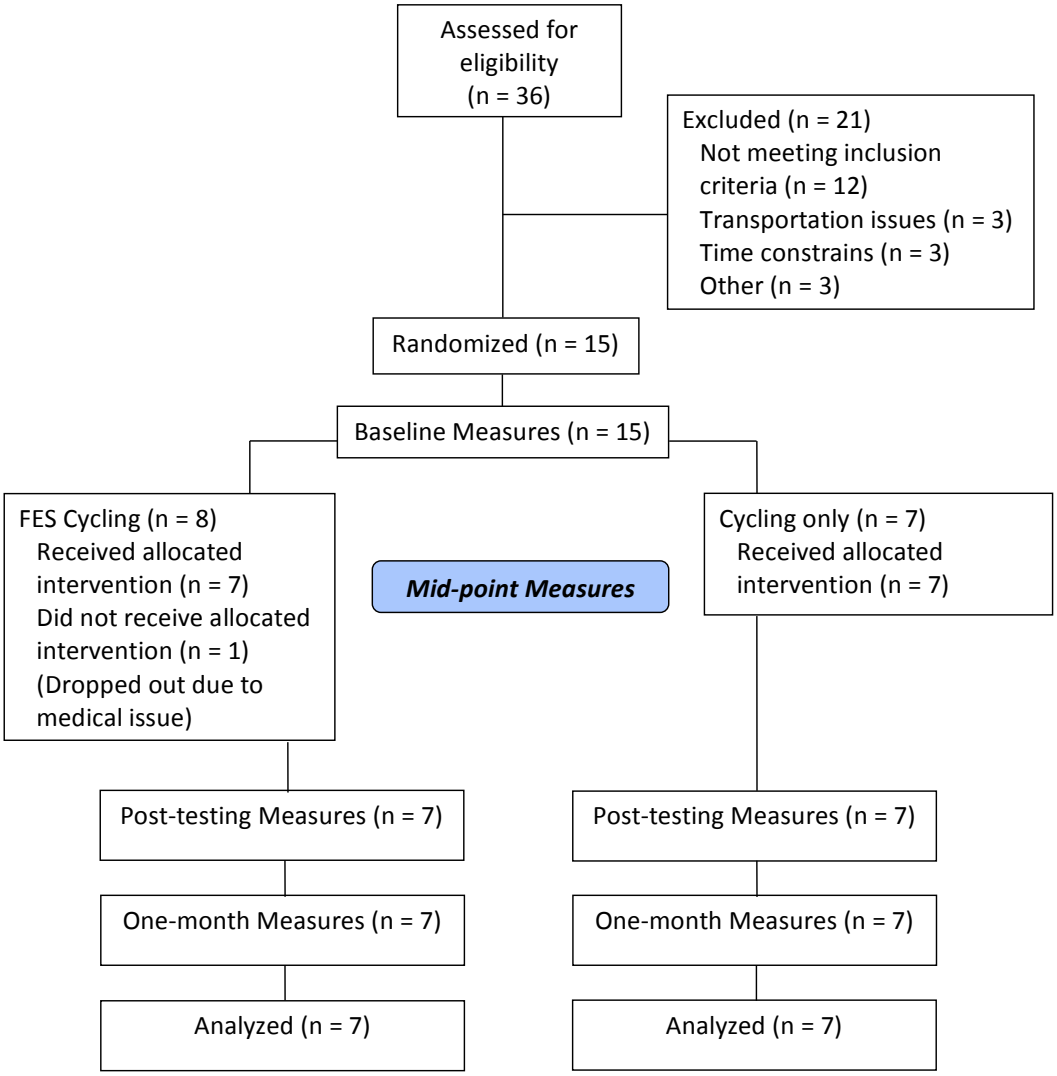


Table 4-1 Baseline Demographics, Characteristics, Selected Clinical and Self-Report Measures

	Overall	FES Cycling	Cycling Only	P Value
Total, n	14	7	7	
Age, years **Mean(SD)** **Median** **Range**	 53.64(10.16) 54.5 30-68	 59.71(7.54) 58 48-68	 47.51(8.97) 49 30-57	t_{12} = 2.17, p = 0.018[a]
Gender, n **Male** **Female**	 6 (43%) 8 (57%)	 4 (57%) 3 (43%)	 2 (13%) 5 (72 %)	
PDDS **Mean(SD)** **Median** **Range**	 3.71(0.91) 3.5 3-6	 3.71(0.76) 4 3-5	 3.71(1.11) 3 3-6	U = 22, p = 0.81[b]
GLTQ **Mean(SD)** **Median** **Range**	 21.57(28.65) 8 0-88	 29.86(33.18) 24 0-88	 13.29(22.75) 6 0-64	U = 17.5, p = 0.38[b]
MoCA **Mean(SD)** **Median** **Range**	 26.43(2.13) 26.5 22-29	 27.0(1.41) 27 25-29	 25.86(2.67) 26 22-29	U = 18.5, p = 0.46[b]
Years since dx **Mean(SD)** **Median** **Range**	 13.14(12.08) 10 3-46	 14.0(14.61) 10 3-46	 12.29(10.05) 10 4-\34	t_{12} = -0.256 p = 0.80[a]
Assistive Device Use (yes/no)	4/10 (28.6%)	3/4 (75%)	1/6 (16.7%)	

Abbreviations: SD = standard deviation, FES = Functional Electrical Stimulation, PPDS = Patient Determined Disease Steps, GLTQ = Godin Leisure-Time Questionnaire, MoCA = Montreal Cognitive Assessment, dx=diagnosis
a = as determined by independent sample t-tests
b =as determined by Mann-Whitney U tests

Baseline outcomes for clinical and self-report outcome measures for the overall sample, FES group, and Cycling Only group are presented in Table 4-2. There was no significant difference between groups on all clinical and self-report measure ($p > 0.05$). The 5XSST approached statistical significance with the Cycling Only group demonstrating better performance (i.e. shorter times) than the FES group ($t_{12} = 2.069$, $p = 0.061$).

Table 4-2 Baseline Group Comparison of Clinical and Self-Report Measures

	Overall	FES Cycling	Cycling Only	P Value
Total, n	14	7	7	
6MWT (m)				
Mean(SD)	362.32(118.32)	357.18(141.21)	367.46(101.65)	$t_{12} = 0.16$,
Median	352.04	366.7	337.4	$p = 0.88$ [a]
Range	143.86-553.21	143.87-553.21	202.39-508.71	
T25FW (m/s)				
Mean(SD)	1.37(0.43)	1.33(0.53)	1.40(0.34)	$t_{12} = 0.30$,
Median	1.421	1.39	1.48	$p = 0.77$ [a]
Range	0.624-2.05	0.62-2.05	0.75-1.71	
TUG (s)				
Mean(SD)	11.39(5.18)	13.05(6.25)	9.73(3.52)	$t_{12} = 1.22$,
Median	9.615	10.73	9.2	$p = 0.25$ [a]
Range	5.97-24.26	5.97-24.26	6.89-17.38	
5XSST (s)				
Mean(SD)	15.12(4.07)	17.14(4.52)	13.11(2.45)	$t_{12} = 2.07$,
Median	15.04	18.6	14.7	$p = 0.06$ [a]
Range	9.57-21.71	10-21.71	9.57-15.21	
MSWS-12				
Mean(SD)	40.78(11.40)	38.71(10.84)	42.86(12.42)	U = 20.5,
Median	44	33	48	$p = 0.62$ [b]
Range	24-57	25-54	24-57	
ABC				
Mean(SD)	58.29(24.31)	64.42(24.42)	52.64(24.57)	U = 16.5,
Median	58.44	77.5	57.5	$p = 0.32$ [b]
Range	18.75-85	28.75-85	18.75-84.38	
MFIS				
Mean(SD)	44.57(15.44)	42.00(12.49)	47.14(18.58)	U = 20.5,
Median	42.5	38	52	$p = 0.62$ [b]
Range	16-74	28-59	16-74	
MSQOL-54				
Overall	59.40 ± 17.08	61.10 ± 16.83	47.57 ± 8.98	U = 20.5,
Mean ± SD	60.84	63.33	58.33	$p = 0.620$ [b]
Median	23.3-81.67	36.67-81.67	23.33-78.33	
Range				

Abbreviations: SD = standard deviation, FES = Functional Electrical Stimulation, 6MWT = 6 Minute Walk Test, T25FW = Timed 25-Foot Walk, TUG = Timed Up and Go, 5XSST = 5 times sit to stand, MSWS-12 = 12-item Multiple Sclerosis Walking Scale, ABC = Activities-specific Balance Confidence Scale, MFIS = Modified Fatigue Impact Scale, MSQOL-54 = Multiple Sclerosis Quality of Life Inventory
a = as determined by independent sample t-tests
b =as determined by Mann-Whitney U tests

Cycling Outcomes

Data for each of the 24 training sessions were collected in the RT300 SAGE controller. During data analysis, each participant's first cycling session was excluded to allow for adjustment to the equipment and procedures. In order to compare starting cycling performance to final cycling performance, the average of three sessions was calculated for the purpose of data analysis (starting performance = sessions 2-4; final cycling performance = sessions 22-24). This was done to account for variability in fatigue from session-to-session that may impact performance.

Starting cycling mileage and starting cycling power output for the FES and Cycling Only groups were compared using an independent t-test and no significant difference was found between groups at the start of the training period (t_{12} = 0.88, p = 0.40; t_{12} = -0.51, p = 0.62). Final cycling mileage and final cycling power output for the FES and Cycling Only groups were compared using an independent t-test and no significant difference was found between groups at the end of the training period (t_{12} = 0.57, p = 0.58; t_{12} = -0.54, p= 0.60). FES and Cycling Only outcomes for mileage and power output are presented in Table 4-3 and 4-4.

Using a paired t-test, no significant difference was found between starting and final cycling mileage for either the FES and Cycling Only group (t_6 = -1.14, p = 0.30; t_6 = 1.47, p = 0.19). A small effect size was found for mileage for both the FES group and Cycling Only group (d = 0.30; d = 0.24). However, there was a significant difference found for change in cycling power output for both the FES group and Cycling Only group (t_6 = -2.88, p = 0.03, p < 0.05; t_6 = -4.46, p = 0.004). A medium effect size for cycling power output was found for the FES group and Cycling Only group (d = 0.66; d = 0.72). Using a two-way ANOVA, no

significant difference was found between groups for mileage and cycling power output ($F_{12} = 0.80$, $p = 0.38$; $F_{12} = 3.28$, $p = 0.08$). Increases in cycling mileage and cycling power output across the training sessions are displayed in Figure 4-2 and 4.3.

Table 4-3 Cycling outcomes for mileage within and between groups

Mileage	FES Cycling	Cycling Only	P[c] Btw time intervals	P[d] Btw Starting and Final intervals
	Mean(SD) 95% CI			
Starting	8.83(1.63)	9.76(2.28)	$t_{12} = 0.88$, $p = 0.40$	
Final	9.66(1.70)	10.36(2.72)	$t_{12} = 0.57$, $p = 0.58$	
Change	0.83	0.6		$F_{12} = 0.80$, $p = 0.38$[d]
P[a] Within group diff. btw start and final	$t_6 = -1.14$, $p = 0.30$[a]	$t_6 = -1.47$, $p = 0.19$[a]		
Effect Size[b] (Cohen's *d*)	0.30	0.24		

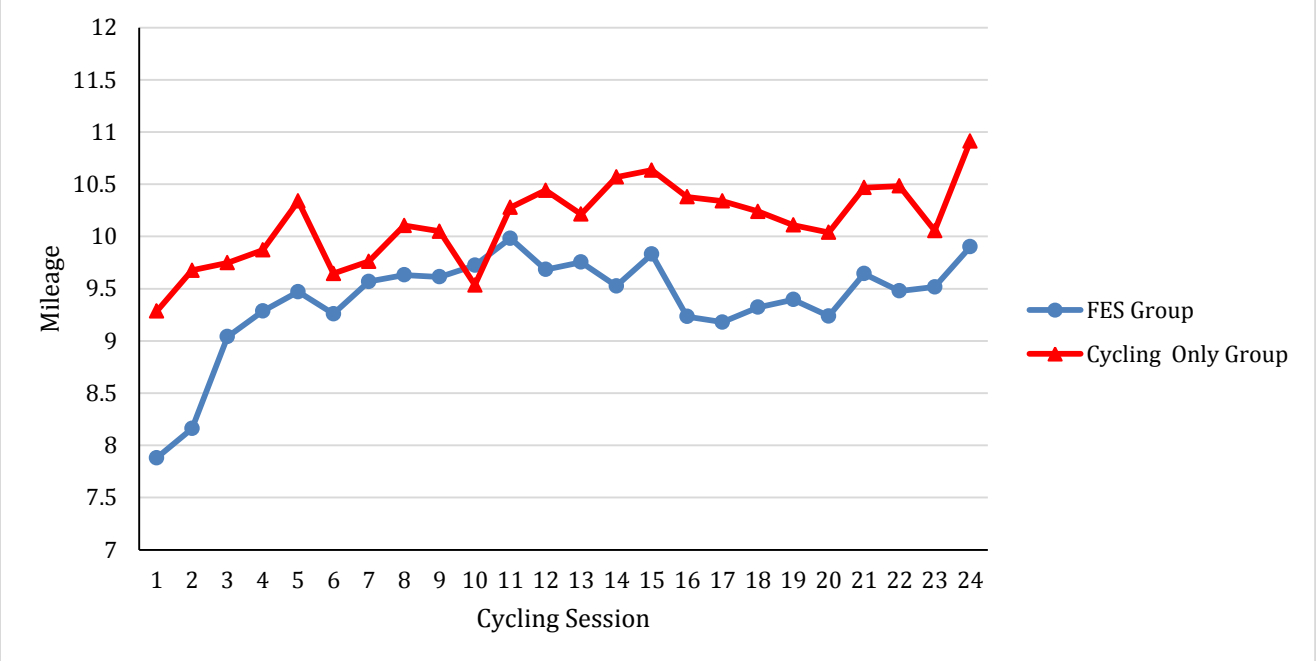
Abbreviations: SD = Standard Deviation, FES = Functional Electrical Stimulation, Btw = between
a = p-value is comparison between starting and final time periods within group using paired t-test
b = Effect Size calculated using the starting and final cycling averages
c = p-value is comparison between groups at time periods using an independent t-test
d = p-value is the overall difference between starting and final time periods using a two-way ANOVA

Table 4-4 Cycling outcomes for cycling power output within and between groups

Power Output (Watts)	FES Cycling	Cycling Only	P[c] Btw time intervals	P[d] Btw Starting and Final intervals
	Mean(SD) 95% CI			
Starting	37.77(18.60)	33.32(13.83)	$t_{12} = -.51$, $p = 0.62$	
Final	52.12(24.30)	45.71(19.94)	$t_{12} = -0.54$, $p = 0.60$	
Change	14.35	12.39		$F_{12} = 3.28$, $p = 0.08$ [d]
P[a] Within group diff. btw start and final	$t_6 = -2.88$, $p = 0.03$*	$t_6 = -4.46$, $p = 0.004$*		
Effect Size[b] (Cohen's *d*)	0.66	0.72		

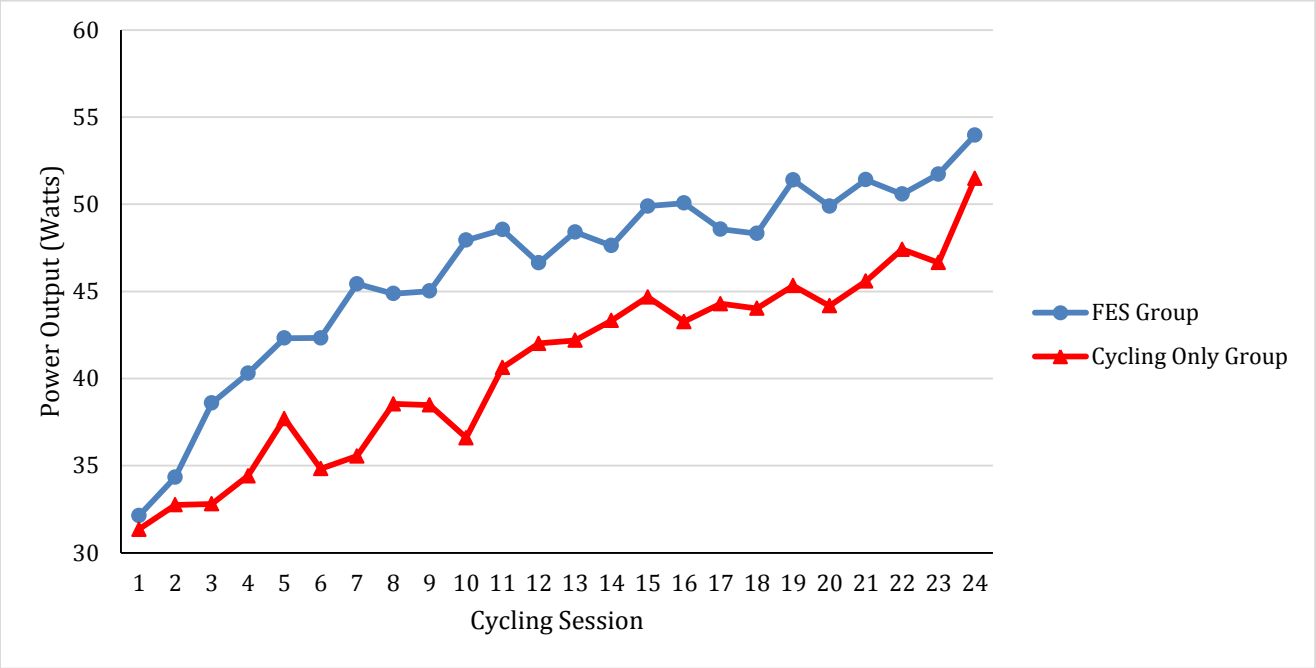
Abbreviations: SD= Standard Deviation, FES = Functional Electrical Stimulation, Btw = between
a = p-value is comparison between starting and final time periods within group using paired t-test
b = Effect Size calculated using the starting and final cycling averages
c = p-value is comparison between groups at time periods using an independent t-test
d = p-value is the overall difference between starting and final time periods using a two-way ANOVA

Figure 4-2 Average Cycling Mileage by Group (FES and Cycling Only) Across Training Sessions



Abbreviations: FES = Functional Electrical Stimulation

Figure 4-3 Average Cycling Power Output by Group (FES and Cycling Only) Across Training Sessions



Abbreviations: FES = Functional Electrical Stimulation

Outcomes Measures: Clinical and Self-Report Measures

Research Question 1

Is there a difference in aerobic capacity as measured by the 6 Minute Walk Test (6MWT) between FES Cycling and Cycling Only training in PWMS?

Results for the 6MWT for the intervention groups as a function of walking distance in meters are presented in Table 4-5. There was a main effect for time ($F(1,12) = 3.90$, $p = 0.02$), but no main effect between groups ($F(1,12) = 0.04$, $p = 0.84$). In addition, there was no interaction of group x time ($F(1,12) = 0.08$, $p = 0.97$). The effect sizes for the FES and Cycling Only groups were small ($d = 0.19$; $d = 0.30$).

Table 4-5 6MWT Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

6MWT (m)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95% CI				
Baseline	357.18(54.34) 246.98-467.38	367.46(54.34) 257.26-477.66			0.89
Mid-point	376.54(54.34) 266.33-486.74	395.85(54.3) 285.65-506.05			0.80
Post-intervention	385.09(54.34) 274.89-495.3	405.49(54.34) 295.29-515.70			0.79
Follow-up	393.37(54.34) 283.16-503.57	406.82(54.34) 296.62-517.02			0.86
Change over Training Period[a]	27.91	38.03	F = 0.04, p = 0.84	F = 3.90, p = 0.02*	
Training Effect Size[e] (Cohen's *d*)	0.19	0.30			

Abbreviations: 6MWT = 6 Minute Walk Test, m = meters, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error, CI = Confidence Interval
a = Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = Effect Size calculated using the baseline and post-intervention means

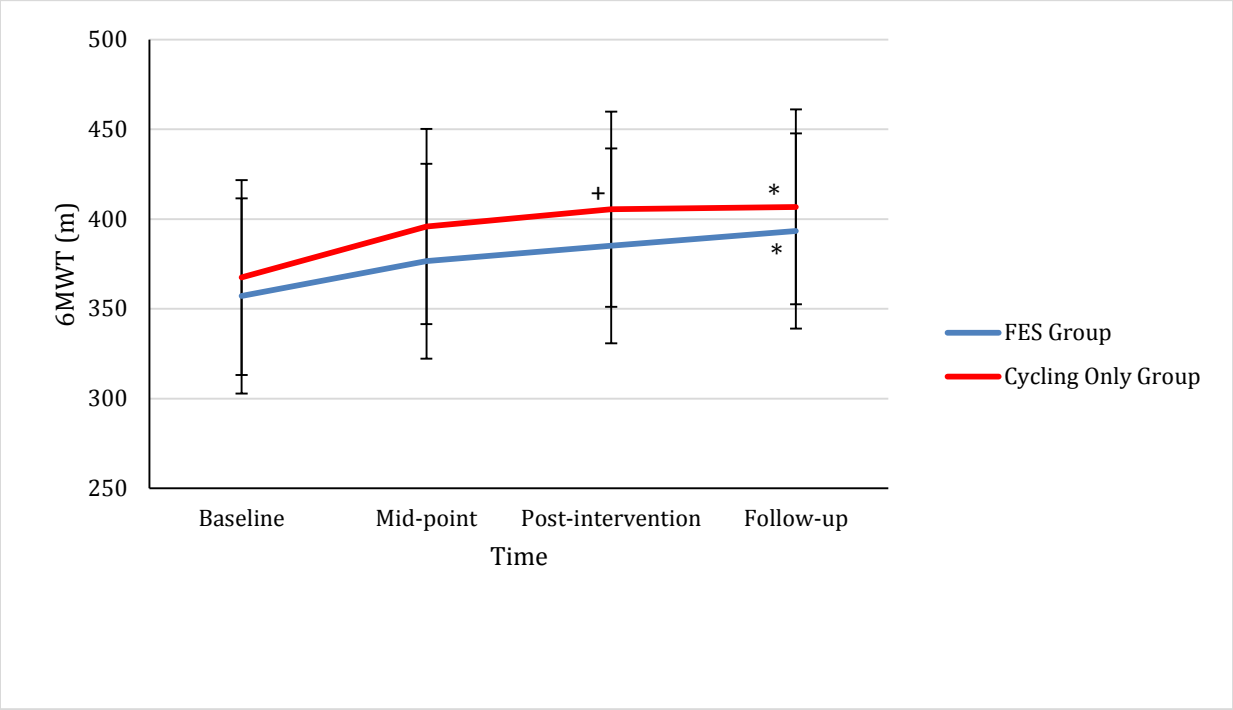
Within group findings for the 6MWT for the FES and Cycling Only groups are presented in Table 4-6 and Figure 4-4. The FES and Cycling Only group had a significant increase in walking distance from baseline to post-intervention (p = 0.04; p = 0.03). The Cycling Only group also showed a significant increase from baseline to follow-up (p = 0.03).

Table 4-6 Within group differences for 6MWT based on the mixed-effect model

6MWT		
	FES Cycling	**Cycling Only**
Baseline - Mid-point	**NS**	**NS**
Baseline - Post-intervention	**0.04**	**0.03**
Baseline - Follow-up	**NS**	**0.03**
Mid-point - Post-intervention	**NS**	**NS**
Mid-point - Follow-up	**NS**	**NS**
Post-intervention - Follow-up	**NS**	**NS**

Abbreviations: FES = Functional Electrical Stimulation, 6MWT = 6 Minute Walk Test

Figure 4-4 6MWT change by group (FES and Cycling Only) over time (Baseline, Mid-point, Post-intervention, Follow-up) (mean ± SE)



Abbreviations: 6MWT = 6 Minute Walk Test, FES = Functional Electrical Stimulation, SE = Standard Error
* denotes significance from baseline to follow-up
+ denotes significance from baseline to post-intervention

Research Question 2

Is there a difference in gait speed as measured by the Times 25-Foot Walk (T25FW) between FES Cycling and Cycling Only training in PWMS?

Results for the T25FW for the intervention groups as a function of gait speed in meters are presented in Table 4-7. There was no main effect for group or time (F (1,12) =1.09, p = 0.37; F (1,12) = 0.35, p = 0.85, respectively). Training effect size within each group was small (*d* = 0.11; *d* = 0.12).

Table 4-7 T25FW Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

T25FW (m/s)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95% CI				
Baseline	1.33(0.18) 0.97-1.70	1.40(0.18) 1.04-1.76			0.78
Mid-point	1.34(0.18) 0.98-1.70	1.42(0.18) 1.05-1.78			0.75
Post-intervention	1.39(0.18) 1.03-1.75	1.45(0.18) 1.09-1.8			0.82
Follow-up	1.44(0.18) 1.08-1.80	1.42(0.18) 1.06-1.78			0.93
Change over Training Period[a]	0.06	0.05	F = 1.09, p = 0.37	F = 0.3, p = 0.85	
Effect Size[e] (Cohen's *d*)	0.11	0.12			

Abbreviations: T25FW = Timed 25-Foot Walk, m/s= meters per second, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error, CI = Confidence Interval
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = Effect Size calculated using the baseline and post-intervention means

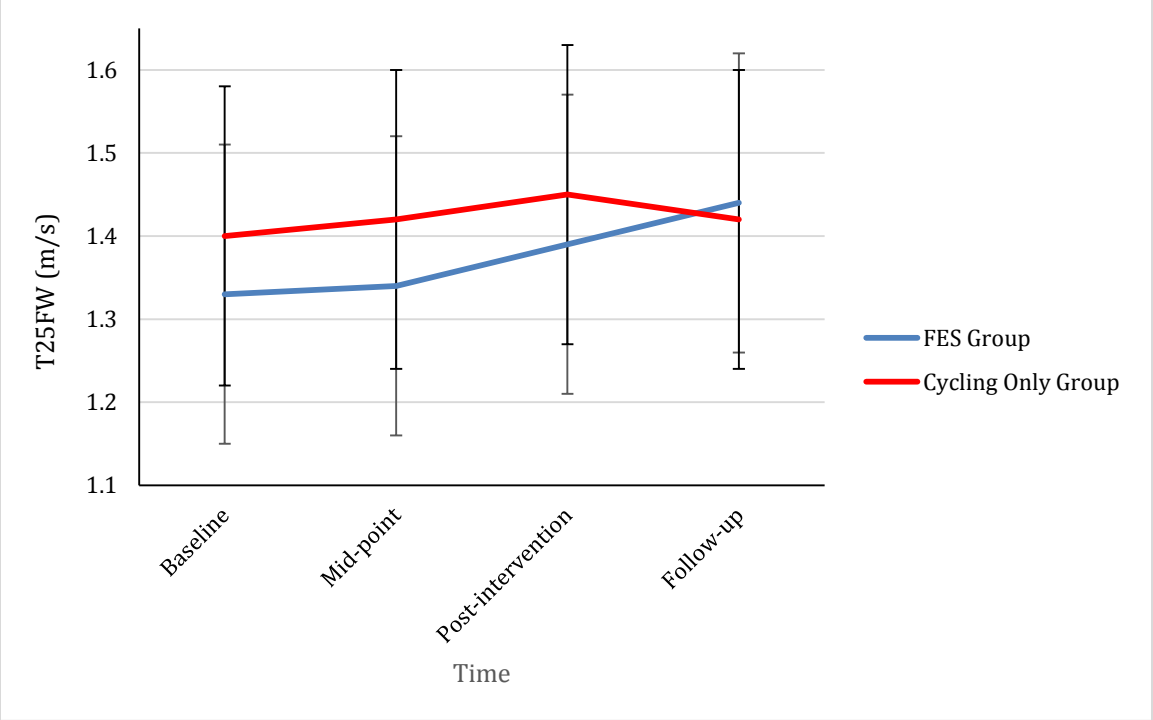
Within group findings for the T25FW for the FES Cycling and Cycling Only groups are presented in Table 4-8 and Figure 4-5. There was no significant change in gait speed for either group, during any time period.

Table 4-8 Within group differences for T25FW based on the mixed-effect model

T25FW		
	FES Cycling	**Cycling Only**
Baseline - Mid-point	**NS**	**NS**
Baseline - Post-intervention	**NS**	**NS**
Baseline - Follow-up	**NS**	**NS**
Mid-point - Post-intervention	**NS**	**NS**
Mid-point - Follow-up	**NS**	**NS**
Post-intervention - Follow-up	**NS**	**NS**

Abbreviations: FES = Functional Electrical Stimulation, T25FW = Timed 25-Foot Walk

Figure 4-5 T25FW change by group (FES and Cycling Only) over time (Baseline, Mid-point, Post-intervention, Follow-up) (mean ± SE)



Abbreviations: T25FW = Time 25-Foot walk, FES = Functional Electrical Stimulation, SE = Standard Error

Research Question 3

Is there a difference in functional lower extremity strength as measured by the 5 Times Sit-to-Stand (5XSST) between FES Cycling and Cycling Only in PWMS?

Results for the 5XSST for the intervention groups as a function of time in seconds are presented in Table 4-9. There was a main effect for time (F (1,12) =11.82, p = 0.001),

but no main effect for group (F (1,12) = 2.10, p = 0.17). In addition, there was a significant interaction of group X time (F (1,12) = 4.29, p = 0.011) (Figure 4.6). A medium training effect size for the 5XSST was found for the FES group and Cycling Only groups (*d* = 0.675; *d* = 0.534).

Table 4-9 5XSST Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

5XSST (sec)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95% CI				
Baseline	17.14(1.28) 14.54-19.73	13.11(1.28) 10.52-15.71			0.03*
Mid-point	14.89(1.28) 12.30-17.48	12.53(1.28) 9.94-15.13			0.20
Post-intervention	14.33(1.28) 11.73-16.92	11.70(1.28) 9.11-14.30			0.16
Follow-up	13.52(1.28) 10.92-16.11	12.44(1.28) 9.85-15.03			0.56
Change over Training Period[a]	-2.81	-1.41	F = 2.10, p = 0.17	F = 11.82, p <0.001*	
Training Effect Size[e] (Cohen's *d*)	0.68	0.53			

Abbreviations: 5XSST = 5 times sit to stand, sec = seconds, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error, CI = Confidence Interval
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = Effect Size calculated using the baseline and post-intervention means

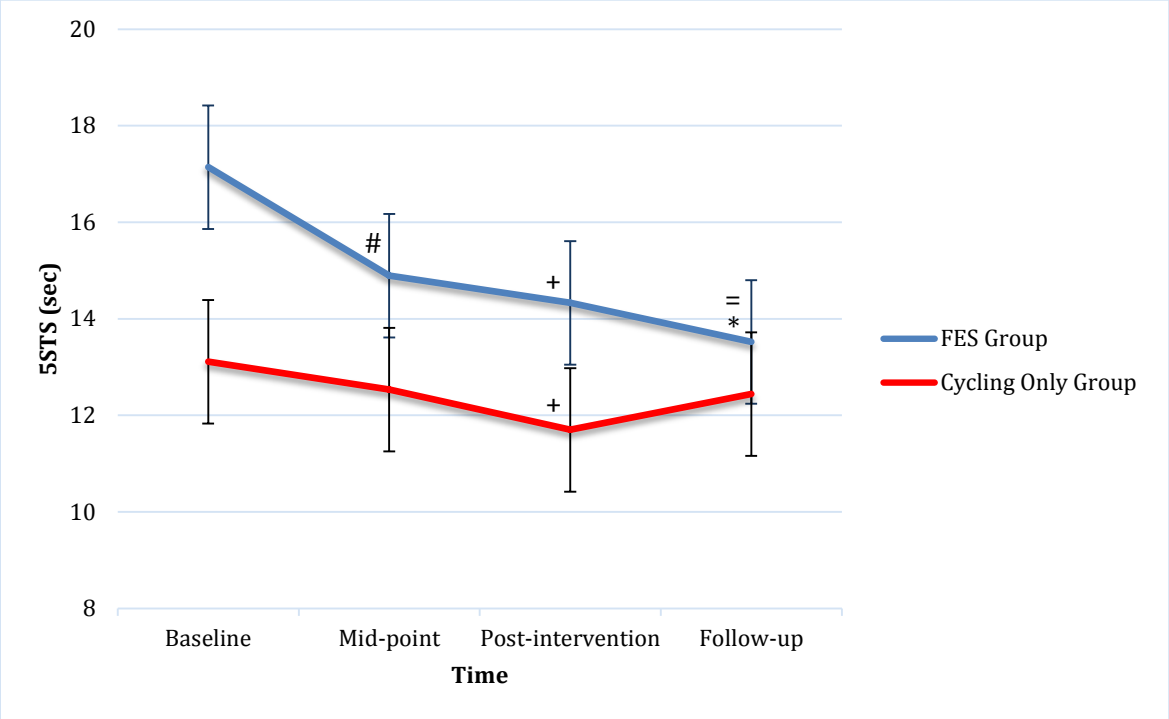
Table 4-10 Within group differences for 5XSST based on the mixed-effect model

5XSST		
	FES Cycling	**Cycling Only**
Baseline - Mid-point	**0.0005**	**NS**
Baseline - Post-intervention	**<0.0001**	**0.02**
Baseline - Follow-up	**<0.0001**	**NS**
Mid-point - Post-intervention	**NS**	**NS**
Mid-point - Follow-up	**0.02**	**NS**
Post-intervention - Follow-up	**NS**	**NS**

Abbreviations: FES = Functional Electrical Stimulation, 5XSST = 5 times sit to

Within group findings for the 5XSST for the FES Cycling and Cycling Only groups are presented in Table 4-10 and Figure 4-6. Using the mixed-effects model, there was a significant difference between groups ($p = 0.03$) at baseline, with the Cycling Only group demonstrating better performance (i.e., lower scores demonstrating faster speed). In both FES and Cycling Only groups there was a significant decrease in 5XSST time between baseline and post-intervention ($p < 0.0001$ and $p = 0.021$, respectively). The FES group also showed significant changes from the baseline to mid-point, from the baseline to follow-up, and from the mid-point to follow-up time periods ($p = 0.0005$, $p < 0.0001$, $p = 0.024$, respectively).

Figure 4-6 5XSST change by group (FES and Cycling Only) over time (Baseline, Mid-point, Post-intervention and Follow-up) (mean ± SE),



Abbreviations: 5XSST = 5 Times Sit to Stand, FES = Functional Electrical Stimulation, SE = Standard Error
# denotes significance from baseline to mid-point
+ denotes significance from baseline post-intervention
* denotes significance from baseline to follow-up
= denotes significance from mid-point to follow-up

Research Question 4

Is there a difference in functional mobility as measured by the Timed up and Go (TUG) between FES Cycling and Cycling Only in PWMS?

Results for the TUG for the intervention groups as a function of time in seconds are presented in Table 4-11. There was no main effect for time or group ($F(1,12) = 1.89$, $p = 0.16$; $F(1,12) = 0.47$, $p = 0.51$, respectively). There was a significant interaction of group x time ($F(1,12) = 4.00$, $p = 0.02$). The effect sizes for the FES and Cycling Only groups were small ($d = 0.30$; $d = 0.03$).

Table 4-11 TUG Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

TUG (sec)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95% CI				
Baseline	13.05(1.89) 9.22-16.88	9.73(1.89) 5.90-13.56			0.22
Mid-point	11.54(1.89) 7.71-15.37	9.53(1.89) 5.70-13.36			0.46
Post-intervention	11.29(1.89) 7.45-15.12	10.38(1.89) 6.55-14.21			0.74
Follow-up	11.15(1.89) 7.32-14.98	10.17(1.89) 6.34-14.00			0.72
Change over Training Period[a]	-1.76	0.65	F = 0.47, p = 0.51	F = 1.89, p = 0.16	
Training Effect Size[e] (Cohen's *d*)	0.30	0.15			

Abbreviations: TUG = Timed Up and Go, sec = seconds, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error, CI = Confidence Interval
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = Effect Size calculated using the baseline and post-intervention means

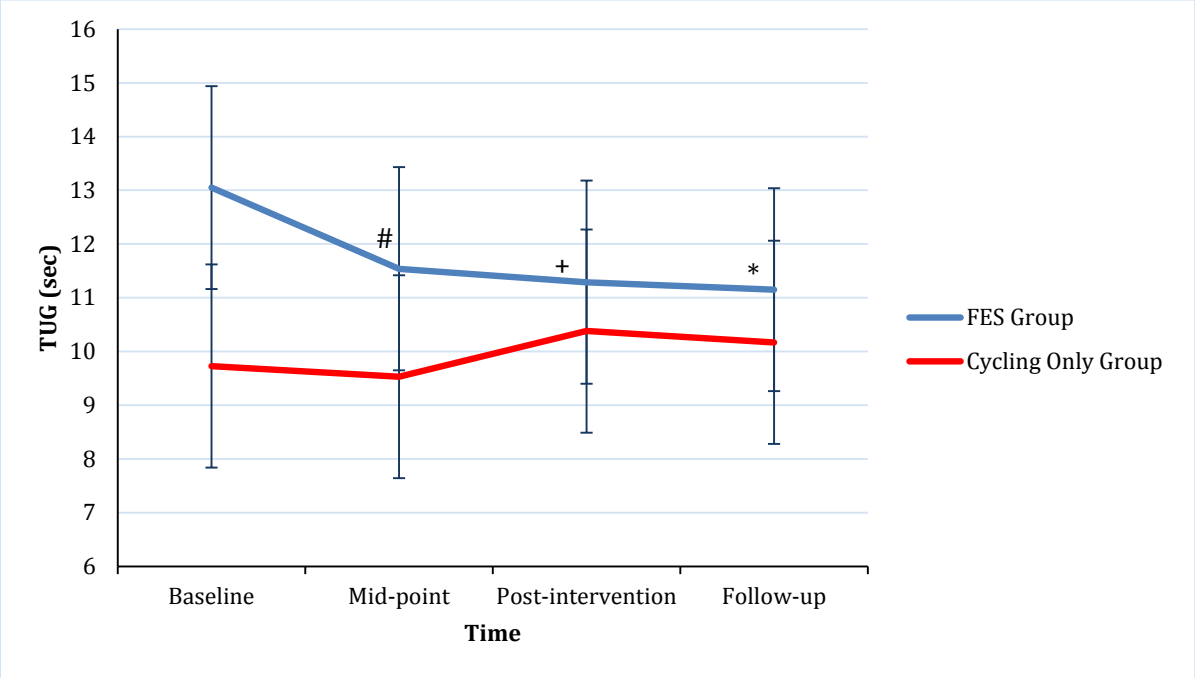
Within group findings for the TUG for the FES Cycling and Cycling Only groups are presented in Table 4-12 and Figure 4-7. Only the FES group demonstrated significant improvements from baseline to mid-point, post-intervention, and follow-up, but changes were not great enough to demonstrate a significant group effect (p=.01, p = 0.004, p =.002, respectively).

Table 4-12 Within group differences for TUG based on the mixed-effect model

TUG		
	FES Cycling	**Cycling Only**
Baseline - Mid-point	**0.01**	**NS**
Baseline - Post-intervention	**0.004**	**NS**
Baseline - Follow-up	**0.002**	**NS**
Mid-point - Post-intervention	**NS**	**NS**
Mid-point - Follow-up	**NS**	**NS**
Post-intervention - Follow-up	**NS**	**NS**

Abbreviations: FES = Functional Electrical Stimulation, TUG = Timed Up and Go

Figure 4-7 TUG change by group (FES and Cycling Only) over time (Baseline, Mid-point, Post-intervention, Follow-up) (mean ± SE)



Abbreviations: TUG = Times Up and Go, FES = Functional Electrical Stimulation, SE = Standard Error
# denotes significance from baseline to mid-point
+ denotes significance from baseline post-intervention
* denotes significance from baseline to follow-up

BTS G-Walk® results for the TUG for the intervention groups are presented in Table 4-13. There was no main effect between groups for all parameters. There was a main effect for time for TUG End-turning phase duration ($F(1,12) = 4.78$, $p<0.007$). All other comparisons and interactions were not significant.

Within group difference at each of the time periods and are available in appendix O and described below. The Cycling Only group demonstrated a significant difference in the TUG Sit to Stand Phase Duration at baseline to post-intervention, mid-point to post-intervention, and post-intervention to follow-up periods demonstrating a greater improvement in performance ($p= 0.05$, 0.01, and 0.001, respectively). The Cycling Only group also demonstrated a significant difference in the TUG Stand to Sit Phase Duration at the mid-point to post-intervention demonstrating a greater improvement in performance ($p = 0.04$). The FES group demonstrated a significant difference in the TUG Mid-Turning Phase Duration at baseline to post-intervention and baseline to follow up (0.02 and 0.001), and the Cycling Only group demonstrated a significant difference from baseline to mid-point. No significant differences in End-Turning were seen at any time period for either group.

Table 4-13 TUG Spatiotemporal outcomes from the BTS G-Walk® at Baseline, Mid-point, Post-intervention, and One-month follow-up based on the mixed-effect model

TUG- Sit to Stand Phase Duration (s)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.12(0.13) 0.85-0.13	1.30(0.13) 1.04-1.56			0.34
Mid-point	1.36(0.13) 1.10-1.61	1.12(0.13) 0.87-1.38			0.20
Post-intervention	1.16(0.13) 0.90-1.41	1.51(0.13) 1.24-1.79			0.06
Follow-up	1.16(0.13) 0.91-1.42	1.00(0.13) 0.74-1.26	F = 0.10, P = 0.76	F = 2.12, p = 0.11	0.36
Change over Training Period[a]	0.04	0.21	.		
TUG- Mid-Turning Phase Duration (s)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	3.86(0.61) 2.63-5.10	2.91(0.57) 1.75-4.07			0.26
Mid-point	4.41(0.57) 3.26-5.57	4.02(0.57) 2.86-5.17			0.63
Post-intervention	4.25(0.57) 3.09-5.40	2.47(0.61) 1.23-3.71			0.04*
Follow-up	3.20(0.57) 2.04-4.35	3.22(0.57) 2.06-4.37	F = 1.81, p = 0.20	F = 1.73, p = 0.18	0.98
Change over Training Period[a]	0.39	-0.44			

TUG- End-turning Phase Duration (s)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	2.93(0.62) 1.66-4.21	2.00(0.61) 0.76-3.23			0.29
Mid-point	2.01(0.61) 0.77-3.25	1.07(0.61) -0.17-2.31			0.28
Post-intervention	1.77(0.61) 0.53-3.01	1.43(0.62) 0.15-2.70			0.70
Follow-up	1.29(0.61) 0.06-2.53	1.29(0.61) 0.05-2.53	F =0.51, p = 0.49	F = 4.78, p<.007*	1.00
Change over Training Period[a]	-1.16	-0.57			
TUG- Stand to Sit Phase Duration (s)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.82(0.23) 1.35-2.29	1.80(0.22) 1.36-2.24			0.95
Mid-point	1.86(0.22) 1.41-2.30	1.70(0.22) 1.26-2.14			0.61
Post-intervention	1.91(0.22) 1.47-2.36	1.53(0.23) 1.05-2.00			0.23
Follow-up	2.29(0.22) 1.84-2.73	1.54(0.22) 1.10-1.99	F = 2.0, p = 0.18	F = 0.32, p = 0.81	0.02*
Change over Training Period[a]	0.09	-0.27			

Abbreviations: TUG = Timed Up and Go, s = seconds, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = Effect Size calculated using the baseline and post-intervention means

Spatiotemporal Outcomes

Research Question 5

Is there a difference on spatiotemporal components of gait between FES Cycling and Cycling Only in PWMS?

Results for spatiotemporal parameters for the 6MWT and T25FW for the intervention groups are presented in Table 4-14 and 4-15. There was no main effect between groups for all parameters except for the 6MWT where there was a main effect for time for Left and Right Stride Length ($F(1,12) = 3.56$, $p = 0.02$; $F(1,12) = 3.43$, $p = 0.03$). Within group differences on spatiotemporal gait parameters based on the mixed-effect model are presented in appendix P and Q. There were limited amounts of within group differences that were found to be significant. The only significant finding was for the 6MWT, where the Cycling Only group demonstrated significant changes in right stride length and left stride length over time from baseline to mid-point, baseline to post-intervention, and baseline to follow-up.

Table 4-14 6MWT Spatiotemporal outcomes from BTS G-Walk® at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

6MWT- Stride Length-Left (m)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.53(0.10) 1.32-1.74	1.44(0.10) 1.23-1.65			0.56
Mid-point	1.55(0. 10) 1.34-1.76	1.54(0.10) 1.33-1.76			0.96
Post-intervention	1.56(0.24) 1.35-1.77	1.56(0.10) 1.35-1.77			0.99
Follow-up	1.55(0.10) 1.34-1.76	1.59(0.10) 1.38-1.80	F = 3.56, p = 0.92	F = 3.56, p = 0.02*	0.79
Change over Training Period[a]	-0.01	0.12			
6MWT- Stride Length-Right (m)	**FES Cycling**	**Cycling Only**	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.53(0.10) 1.32-1.74	1.44(0.10) 1.23-1.65			0.54
Mid-point	1.55(0.10) 1.34-1.76	1.54(0.10) 1.33-1.76			0.97
Post-intervention	1.57(0.10) 1.36-1.78	1.56(0.10) 1.35-1.77			0.95
Follow-up	1.54(0.10) 1.34-1.75	1.59(0.10) 1.38-1.80	F = 0.01. p = 0.92	F = 3.43, p = 0.03*	0.77
Change over Training Period[a]	0.00	0.12			

6MWT- Step Symmetry[e]	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.00(0.03) 0.94-1.05	1.03(0.03) 0.98-1.09			0.35
Mid-point	1.03(0.03) 0.98-1.08	0.99(0.03) 0.92-1.05			0.30
Post-intervention	0.98(0.03) 0.92-1.04	1.00(0.03) 0.95-1.07			0.49
Follow-up	1.01(0.03) 0.96-1.07	1.01(0.03) 0.95-1.07	F = 0.05, p = 0.84	F = 0.06, p = 0.98	0.91
Change over Training Period[a]	-.0.02	-0.03			
6MWT- Double-Support- Left (% cycle)	**FES Cycling**	**Cycling Only**	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	14.15(1.46) 11.19-17.12	11.86(1.46) 8.89-14.82			0.274
Mid-point	14.70(1.46) 11.73-17.67	11.65(1.46) 8.45-14.86			0.165
Post-intervention	13.71(1.46) 10.74-16.67	14.25(1.46) 11.28-17.21			0.796
Follow-up	12.18(1.46) 9.22-15.15	13.96(1.46) 10.99-16.92	F = 0.183, p = 0.68	F = 0.580, p = 0.632	0.396
Change over Training Period[a]	-0.44	2.39			

6MWT- Double- Support- Right (% cycle)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	14.94(1.76) 11.37-18.52	12.02(1.76) 8.45-15.60			0.250
Mid-point	15.16(1.76) 11.58-18.74	11.96(1.93) 8.03-15.89			0.229
Post-intervention	14.08(1.76) 10.50-17.66	14.66(1.76) 11.08-18.24	F = 0.171, p = 0.686	F = 0.611, p = 0.613	0.819
Follow-up	11.88(1.76) 8.30-15.46	13.85(1.76) 10.27-17.43			0.435
Change over Training Period[a]	-0.86	2.64			

Abbreviations: FES = Functional Electrical Stimulation, 6MWT = 6 Minute Walk Test, m=meters, SE= Standard Error
a = Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = step symmetry calculated by taking the absolute value of the left step length/right step length

Table 4-15 T25FW Spatiotemporal outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

T25FW – Stride Length-Left (m)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.59(0.10) 1.38-1.80	1.64(0.10) 1.43-1.85			0.76
Mid-point	1.58(0.10) 1.37-1.80	1.62(0.10) 1.41-1.83			0.78
Post-intervention	1.55(0.10) 1.34-1.76	1.64(0.10) 1.42-1.85			0.55
Follow-up	1.52(0.10) 1.31-1.73	1.68(0.10) 1.47-1.90	F = 0.35, p = 0.57	F = 0.23, p = 0.88	0.28
Change over Training Period[a]	-0.04	0.00			
T25FW - Stride Length-Right (m)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.59(0.10) 1.38-1.80	1.63(0.10) 1.42-1.84			0.80
Mid-point	1.57(0.10) 1.36-1.78	1.62 (0.10) 1.41-1.83			0.74
Post-intervention	1.54(0.10) 1.33-1.75	1.64(0.10) 1.43-1.85			0.50
Follow-up	1.52(0.10) 1.31-1.73	1.69(0.10) 1.48-1.90	F = 0.37, p = 0.55	F = 0.32, p = 0.81	0.28
Change over Training Period[a]	-0.05	0.01			

T25FW- Step Symmetry[e] (m)	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	1.02(0.04) 0.95-1.09	1.01(0.04) 0.94-1.08			0.92
Mid-point	1.02(0.04) 0.95-1.09	0.99(0.04) 0.91-1.06			0.52
Post-intervention	0.94(0.04) 0.87-1.01	1.00(0.04) 0.94-1.08			0.17
Follow-up	1.05(0.04) 0.98-1.12	1.02(0.04) 0.95-1.09	F = 1.92, p = 0.19	F = 1.37, p = 0.27	0.65
Change over Training Period[a]	-0.08	0.01			
T25FW - Double-Support- Left	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	13.63(1.52) 10.55-16.7	13.01(1.52) 9.93-16.08			0.77
Mid-point	13.53(1.52) 10.45-16.61	13.43(1.52) 10.36-16.51			0.97
Post-intervention	15.39(1.52) 12.31-18.47	12.60(1.52) 9.53-15.68			0.20
Follow-up	12.80(1.52) 9.73-15.88	12.03(1.52) 8.95-15.11	F = 0.34, p= 0.57	F = 1.08, p = 0.37	0.72
Change over Training Period[a]	1.76	-0.41			

T25FW - Double-Support- Right	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	12.50(1.62) 9.21-15.79	12.06(1.62) 8.76-15.35			0.85
Mid-point	13.31(1.62) 10.02-16.60	13.99(1.62) 10.69-17.28			0.77
Post-intervention	14.97(1.62) 11.67-18.26	13.65(1.62) 10.36-16.95			0.57
Follow-up	12.62(1.62) 9.33-15.91	13.97(1.62) 10.68-17.27	F = 0.001, p = 0.97	F = 1.49, p = 0.23	0.56
Change over Training Period[a]	2.47	1.59			

Abbreviations: FES = Functional Electrical Stimulation, T25FW = Timed 25-Foot Walk, m/s= meters per second, SE = Standard Error
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period
e = step symmetry calculated by taking the absolute value of the left step length/right step length

Self-Report Measures

Research Question 6

Is there a difference on quality of life and self-reported walking and balance measures between FES Cycling and Cycling Only in PWMS?

MSQOL-54

Results for the MSQOL-54 for the invention groups are presented in Table 4-16. There was no significant difference between groups at any specific time period. There was a main effect for time for the MSQOL-54 Mental Composite and MSQOL-54 Overall QOL subscale (F (1,12) = 4.17, p = 0.03; F (1,12) = 5.60, p = 0.01, respectively).

Within group differences for MSQOL-54 are presented in appendix R. Significant changes in the MSQOL-54 Physical Composite for the FES group were present from baseline to post-intervention (p = 0.01) and for Overall Quality of Life from baseline to post-intervention and baseline to follow-up (p = 0.005; p = 0.004, respectively). A within groups difference was also present for the Cycling Only group for the Mental composite from baseline to post-intervention (p = 0.05).

Table 4-16 MSQOL-54 Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

MSQOL-54 Physical Composite	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	50.58(6.66) 36.84-64.32	50.87(6.66) 37.13-64.61			0.98
Post-intervention	61.27(6.66) 47.53-75.01	53.70(6.66) 39.96-67.43			0.43
Follow-up	57.65(6.66) 43.91-71.39	51.19(6.66) 37.45-64.93	F = 0.27, p = 0.06	F = 2.95, p = 0.07	0.50
Change over Training Period[a]	10.49	2.83			
MSQOL-54 Mental Composite	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	67.95(8.54) 50.32-85.58	55.73(8.54) 38.10-73.36			0.32
Post-intervention	77.06(8.54) 59.43-94.69	66.36(8.54) 48.73-83.99			0.39
Follow-up	78.20(8.54) 60.57-95.83	62.53(8.54) 44.90-80.16	F = 1.30, p = 0.28	F = 4.17, p = 0.03*	0.21
Change over Training Period[a]	9.11	10.63			

MSQOL-54 Overall QOL	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	61.19(6.28) 48.24-74.15	57.62(6.28) 44.66-70.57			0.69
Post-intervention	70.95(6.28) 58.00-83.91	60.95(6.28) 48.00-73.91			0.27
Follow-up	71.43(6.28) 58.47-84.39	60.48(6.28) 47.52-73.43	F = 0.93, p = 0.35	F = 5.60, p = 0.01*	0.23
Change over Training Period[a]	9.04	3.33			

Abbreviations: MSQOL-54 = Multiple Sclerosis Quality of Life Inventory, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period

MFIS

Results for the MFIS for the invention groups are presented in Table 4-17. There was no main effect for group on the MFIS Total, but there was a main effect for time ($F(1,12) = 4.08$, $p = 0.03$). There were within group differences group at various time periods for both the FES group and Cycling Only group . From baseline to post-intervention, the Cycling Only group experienced significant changes in the MFIS Cognitive subscore ($p = 0.04$), the FES group experienced changes in the MFIS Physical subscore ($p = 0.01$), and the FES group experienced significant changes in the MFIS total score (p 0.03). There were no significant within group differences for the MFIS (appendix R).

Table 4-17 MFIS Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

MFIS Total	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	42.00(6.19) 29.23-53.77	47.13(6.19) 34.37-59.92			0.56
Post-intervention	32.00(6.19) 19.23-44.77	39.57(6.19) 26.80-52.35			0.40
Follow-up	36.71(6.19) 23.94-49.49	44.29(6.19) 31.51-57.06	F = 0.72, p = 0.41	F = 4.08, p = 0.03*	0.40
Change over Training Period[a]	-10	-7.56			

Abbreviations: MFIS= Modified Fatigue Impact Scale, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error
a =Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period

MSWS-12

Results for the MSWS-12 for the invention groups are presented in Table 4.18. There was no main effect for group or time on the MSWS-12. There were no significant differences within group differences for the MSWS-12 (appendix R).

Table 4-18 MSWS-12 Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

MSWS-12	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	64.43(6.78) 50.44-78.43	71.43(6.78) 57.44-85.42			0.47
Post-intervention	59.51(6.78) 45.52-73.50	69.52(6.78) 55.53-83.52			0.31
Follow-up	60.46(6.78) 46.46-74.45	70.00(6.78) 56.00-83.99	F = 0.95, p = 0.35	F = 0.90, p = 0.42	0.33

Abbreviations: MSWS-12 = 12 item Multiple Sclerosis Walking, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error
a = Calculated by subtracting post-intervention mean from baseline mean
b = p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period

ABC

Results for the ABC for the invention groups are presented in Table 4-19. There was no main effect for group or time on the ABC. There were no within group differences for either group at any time period. There were no significant differences within group differences for the ABC (appendix R).

Table 4-19 ABC Outcomes at Baseline, Mid-point, Post-intervention, and One-month Follow-up based on the mixed-effect model

ABC	FES Cycling	Cycling Only	P[b] Overall Btw Group	P[c] Overall Btw Time	P[d] Btw Group by time
	Mean(SE) 95%CI				
Baseline	64.42(8.63) 46.62-82.23	52.63(8.63) 34.83-70.44			0.34
Post-intervention	70.27(8.63) 88.07-52.46	61.61(8.63) 43.801-79.41			0.49
Follow-up	68.80(8.63) 51.00-86.60	59.08(8.63) 41.27-76.88	F = 0.77, p = 0.40	F = 2.18, p = 0.14	0.43
Change over Training Period[a]	5.85	8.98			

Note. Values are mean ± SE
Abbreviations: ABC = Activities-specific Balance Confidence Scale, FES = Functional Electrical Stimulation, Btw = between, SE = Standard Error
a =Calculated by subtracting post-intervention mean from baseline mean
b= p-value is the overall between groups using a repeated measures analysis of variance
c = p-value is the overall between time periods using a repeated measures analysis of variance
d = p-value is the comparison between the FES cycling and Cycling Only group at each time period

Summary

Fourteen PWMS completed 24 training sessions of either FES cycling or Cycling Only over an 8-10 week training period. Participants reported no adverse events or increases in MS related symptoms (i.e., spasticity, fatigue, pain) during the training period. A few participants reported fatigue after training but conveyed their fatigue levels returned to baseline after rest.

Findings

Medium effect sizes were noted for cycling power output and 5XSST for both the FES cycling and Cycling Only groups. Main effects for time were present for 6MWT and 5XSST, but there were no statistically significant differences found between groups on

any measures. PWMS also experienced improvements in their quality of life as demonstrated by significant improvements in the MFIS over time, the Mental Composite subscale of the MSQOL-54, and the Overall QOL subscale of the MSQOL-54.

Chapter 5

Introduction

This chapter will discuss the results as they relate to walking performance and quality of life in PWMS. Findings will also be compared and contrasted to the current research. Limitations of the current study, clinical implications on physical therapist practice guidelines, and recommendations for future research will be explored.

Discussion of Results

This randomized, clinical pilot study investigated the effects of lower extremity cycling, with and without FES, in ambulatory people with mild to moderate multiple sclerosis (3.0 to 6.0 on the PDDS). This study further adds to the literature supporting that FES Cycling is well-tolerated and beneficial for those with mild to moderate MS.[36,38,102] To my knowledge, this is the only randomized clinical pilot study to examine the effect of FES Cycling versus Cycling Only in PWMS. The current study included people based on their functional classification, whereas some previous FES cycling studies focused on individuals with only specific clinical subtypes of MS.[36,41] Previous studies lacked comparisons or control groups, only stimulated proximal muscle groups, and lacked a strong variety of outcome measures to document changes in walking performance and QOL.[2,34,37,97,166]

One of the primary aims of this study was to examine if there is a difference in scores on clinical and self-report measures when comparing FES Cycling to Cycling Only. Although no overall differences between groups were observed, cycling, in general, was found to have a positive effect on select aspects of aerobic capacity, sit-to-stand, and

quality of life. Although not statistically significant, the FES group showed a trend toward continued improvement at one-month post-training on the 5XSST and the T25FW.

Cycling Outcomes

Overall small changes in mileage were seen within each group. This finding was consistent with expected results since resistance was steadily increased, potentially making it difficult for subjects to increase their overall mileage. Evidence for resistance training in PWMS is well-supported in the literature, and should continue to be included in treatment approaches for PWMS.[85,88]

In the current study, participants in the FES and Cycling Only groups demonstrated significant improvements in cycling power output and, although the mean resistance of the FES group was higher at baseline and at the last training session, there was no statistically significant differences found between groups. Backus et al[38] also found , improvements in cycling power output in a FES cycling study in PWMS in people with severe weakness or paralysis. Combining the results of this current study and Backus et al[38] support that cycling power output using FES is an outcome that can be improved across a wide range of disability levels in PWMS. In contrast, a systematic review by Hunt et al[107] found FES efficiency and cycling power output to be lower when compared to volitional cycling in people with spinal cord injury, stroke, or cerebral palsy. One possible explanation for these differences could the difference in adjustment of stimulation parameters and the amount of voluntary control used by the participants in each of the studies. Based on the findings of this comparison study, the addition of electrical stimulation may allow greater power inputs to be achieved with FES by assisting motor unit recruitment.

Clinical Measures

Aerobic Capacity

Improvements in the 6MWT seen in both the FES cycling and Cycling Only groups were consistent with positive changes seen using the 6MWT in other endurance training studies in PWMS (treadmill, cycling, etc.).[12,15] Janssen et al examined outcomes using FES Cycling versus cycling without stimulation in people with chronic stroke and found that both groups demonstrated improvements on the 6MWT, but no significant differences between groups were found.[27] This is similar to the results of the present study where the addition of stimulation does not appear to significantly improve aerobic capacity more than cycling without stimulation. Improvements in the 6MWT were consistent with other endurance training studies (treadmill, cycling, etc.).[12,15] Using animal models that study autoimmune encephalopathy, researchers demonstrated that endurance exercise may also serve to slow the disease progression and reduce the length of exacerbations.[77] Aerobic exercise may also protect,[78] regenerate, and adapt neuronal processes, which can reduce long-term disability.[46]

Rampello et al[12] had similar findings when using the 6MWT as an outcome when exploring an intensive cycling program for PWMS that focused aerobic training. One of the keys to a successful change in walking endurance in this study, and the Rampello et al may be attributed to the length of the training session, frequency of sessions, and intensity.[12] The training protocol in the current study is similar to Rampello et al where they trained their participants, 3-times per week, for 8 weeks, using 40-minute training sessions and workload up to 80% based on a baseline cardiopulmonary respiratory test.[12] It is well-established that "intensity matters" when looking to make neuroplastic changes

in the central nervous system[45] and fitness levels when comparisons are made between an exercise and control groups in PWMS.[50,80]

Collett et al[16] examined the effects of cycling on PWMS using three different cycling protocols during a 2-times per week for 12 week training protocol that included baseline exercise testing to establish starting workload. In each protocol participants performed the same relative amount of work. Intensities were either continuous (45% of peak power), intermittent (30 seconds on: 30 seconds off at 90% of peak power), or combined (10 min intermittent at 90% peak power, then 10min continuous at 45% peak power). Although no differences were found between groups on the two-minute walk test (2MWT), they found that the intermittent group showed greater improvement at 0 to 6 weeks, though improvement was not statistically significant. The current study used an interval training protocol where participants cycled for 5 minutes against their set workload and then passively cycled 1 minute to recover, supporting that interval training should be considered when working with PWMS. Short rest breaks may allow PWMS to train longer, with less fatigue. Further studies should be conducted to compare interval training to continuous training in PWMS.

In this study, the range of distance covered during the 6MWT varied considerably at baseline, as evidenced by the wide confidence intervals (CI) (FES 95% CI, 246.48-467.38; Cycling Only 95% CI 257.26 – 477.66). Similar results were noted in a study by Collett et al[16] which used the 2MWT as an outcome measure. In the current study, this variability was likely present due to the variability in walking disability of the participants (FES range = 143.86-553.21; Cycling only range = 202.39-508.71). The heterogeneity seen in this sample is common in MS and it is one of the reasons why research in PWMS

can be challenging. Further study examining changes in aerobic capacity using sample sizes with narrower walking performance as inclusion criteria may be indicated so that results can be applied better to individuals of varying disability.

Gait Speed

Gait speed is considered a critical vital sign in clinical practice and is highly correlated with fall risk.[131] It is a critical measure since it has been found that even individuals with mild MS (EDSS 0 - 2.5, with and without pyramidal signs) demonstrate significant changes in gait speed when compared to age and sex matched controls.[172] The current study did not find any significant changes in gait speed in either training group. Ratchford et al[36] is the only other FES cycling study in PWMS to report gait speed as an outcome measure. In their home-based FES cycling study, investigators documented a 36% improvement in the Timed 25-Foot Walk (T25FW). In the Ratchford et al study, individuals were more disabled and trained for 6 months, whereas individuals in the current study were household and community ambulators and trained for 8-weeks.[36] It is possible that there is a greater ability to make changes in gait speed for individuals who demonstrate slower gait speeds at baseline. In a case series examining cycling outcomes in three groups of participants with stroke, the two groups with the slower gait speeds made greater improvements in gait speed after training.[173] Further research needs to be conducted to examine the effect of longer training periods on gait speed in PWMS.
In addition, it is likely that lack of specificity in the training (i.e. cycling vs. walking), impacted a participant's ability to demonstrate a change in this outcome. This is consistent with other cycling studies in stroke where the effect size for gait speed was small after a 3 times per week, 10 week cycling study.[174]

Based on a study by Alon, Conroy and Donner,[23] people with chronic stroke improved their gait velocity by 25% (p = .001), and performed FES Cycling at or close to 60 rpm for 30 minutes for 8 weeks, 3 times per week. Therefore, it may be important to train at higher cycling speeds to see changes in gait speed. The protocol in the current study focused on increasing resistance while participants maintained a minimum speed of 45 rpm. This speed may have not been demanding enough to promote changes in gait in PWMS.

Functional LE Strength

In this study, the 5 Times Sit to Stand (5XSST) was used as a functional measure of lower extremity muscle strength since measuring strength isokinetically is not time efficient in the clinical environment. Although other components of movement (e.g. coordination, balance, range of motion, and sensation) are integral in sit-to-stand movements, in a sample of older adults (mean age = 64.50), McCarthy et al[175] found that lower extremity strength explained 48% of the variance in sit-to-stand. The 5XSST, or similar measures, have not be used in previous FES studies in PWMS, although Fornusek and Hoang[41] reported improvements in self-perceived transfer ability on a standardized rating scale in PWMS who had weak, but voluntary quadricep contractions (EDSS 7.0 - 7.5). In the current study, when compared to baseline, only the FES group demonstrated improvements in the 5XSST at mid-point, post-intervention, and follow-up, whereas the Cycling Only group did not demonstrate improvements until post-intervention. In addition, the FES group demonstrated significant changes continued to show improvement one-month post intervention, whereas the Cycling Only group slightly

declined during this time period. Since both groups were receiving resistance during their cycling, it is possible that the addition of FES assisted in these early changes in muscle strength that were sustained throughout the study period. In people with complete and incomplete SCI, increases in thigh circumference[176] and muscle strength[93] have been documented after FES cycling training. Support for improvements in lower extremity muscle performance was also demonstrated in post-acute stroke where patients received 3 hours total of either standard inpatient therapy or standard therapy plus FES cycling. The FES cycling group demonstrated significant differences in their maximum isometric voluntary contraction of quadriceps, sit-to-stand ability, and the Motricity index.[25]

Functional Mobility

In contrast to Collett et al[16] who found significant change in the Timed Up and Go (TUG) comparing three different intensities of cycling in PWMS, in this study, only the FES group experienced significant changes between time periods (baseline to mid-point, post-intervention, and follow-up), but the changes were not large enough to demonstrate significance within groups differences. The Cycling Only group did not demonstrate a significant change in the TUG during any time period. The TUG is a combination of a sit to stand motion, turning, and short distance walking. It is likely the findings in the FES group were due to the sit to stand motion, which is supported by the findings demonstrated in the 5XSST especially since there were no significant changes found in gait speed nor turning speed. In a progressive resistance cycling protocol combined with balance training, Cakt et al[15] also found significant changes in the TUG, but it is difficult to

determine if cycling or balance training had a greater impact on their results since subjects received a combined intervention.

Spatiotemporal Gait Outcomes

While there are no available studies that measured changes in spatiotemporal gait using cycling protocols, resistance training protocols have demonstrated improvements in step length.[85] Resistance, combined with endurance training, was integral to this study and may have been the reason changes in stride length were present, but does not explain why these changes were only present in the Cycling Only group. The effect size for power output was slightly higher in the Cycling Only group but power output between groups was not statistically significant. Since the task of walking overground was not trained or emphasized, it was expected that minimal changes in spatiotemporal gait parameters were present.

Self-Report Measures

Monitoring quality of life is of great importance in neurodegenerative disease, and self-report QOL measures are underutilized in clinical practice.[177] When reporting QOL in people with a neurodegenerative disease, maintaining QOL, or even a slight improvement, can be meaningful to an individual. Ratchford et al[36] found improvements in the overall SF-36 scores, as well as improvements in the physical and mental health subscores in a cohort of PWMS. In addition, Backus et al[178] found a significant change in the SF-36 social subscale score when utilizing FES cycling in PWMS. After an aerobic training protocol, Rampello et al[12] also found significant changes in three MSQOL-54 subscales (emotional

well-being, energy, and health distress).

In this study, significant changes were found at different time periods on the various subscale of MSQOL-54 (appendix R). Only the FES group showed significant changes in their overall QOL subscale and the physical composite subscale, whereas only the Cycling Only group had changes in mental health composite. Changes in the physical composite might only have been seen in the FES group, since as a group, they were slightly more impaired based on baseline comparisons. Interestingly, neither group had significant changes in the social subscale. Changes in social function may not have been present since changes would have to be large enough to impact an individual's ability to socialize more outside the home.

MS fatigue that is centrally driven by the disease itself or by secondary sources of fatigue such as sleep disturbances, medication side effects, deconditioning, obesity and depression[179] can be positively impacted by exercise in PMWS.[38,54,73] In the current study, both groups experienced significant improvements in their MFIS Total Score and the Physical subscale. It is of great importance that clinicians and researchers continue to measure fatigue using standardized scales since it is one of the perceived barriers to exercise. An exercise intervention that decreases the overall feeling of fatigue, without increasing fatigue, would be a valued contribution.

Additional self-report measures, such as the Activities-specific balance confidence (ABC), and Multiple Sclerosis Walking Scale (MSWS-12), in this study did yield favorable findings. Although scores on the scales did improve, demonstrating improved perception of balance or walking, neither group reached statistical significance. This may have been due to participants not hitting a threshold where they experienced change in their

everyday walking, a lack of specificity of the intervention compared to walking and postural control, or the need to train for longer time periods.

Clinical Implications

Several PWMS who demonstrated changes in performance, indicating that the intervention had a meaningful change in their endurance, mobility, functional leg strength, and/or quality of life. Table 5.1 shows changes from pre-to-post training on measures that have available data for minimal detectable changes (MDC) in other populations. MDCs assist clinicians in setting goals for patients by identifying the smallest change in an outcome that is considered clinically relevant to the patient.[180] Eleven out of 14 participants met the threshold for MDC for one or more measures. Improvements did not appear to follow any specific pattern (e.g. those with greater disability improving more), but this warrants further statistical investigation.

Selecting outcome measures that capture change in function and quality of life are critical when justifying the interventions in the clinical setting. A multidisciplinary panel recommended core outcome measures for exercise studies, which include the MFIS (or Fatigue Severity Scale), 6MWT, TUG, MSQOL-54 (or the MSIS-29), and body mass index.[16,161] Based on the results of this study, additional outcomes measures that should be considered are the T25FW and 5XSST. Based on other studies, the TUG may have questionable value in detecting change.[16,74] The combination of the 5XSST and T25FW may offer additional information since sit to stand and walking speed are captured separately, and may be a good alternative to the TUG. Other measures that may be considered in the clinic would include the 30 second chair stand, as a replacement for the 5XSST, or a 10-meter walk test, as a replacement for the T25FW. The ABC, a self-report

balance measure, is not commonly used in research in the MS population[181] and will likely only show minimal change after a cycling protocol. The MSQOL-54 and MFIS are valuable in assisting clinicians to capture all the facets of MS and the disease progression.[177] The MFIS provides more specific information regarding fatigue, and 42% of the participants in this study reported a significant change (> 19.3%) in their fatigue levels

Based on the both the overall results and individual results of the participants in this study, both FES Cycling and Cycling Only appear to have positive benefits. Conclusions regarding recommendations for cycling mode cannot be made based on the results of this study. Due to the safety, aerobic and strength training benefits of this exercise, cycling should continue to be included in exercise prescription for PWMS. Individuals with more significant disability may also benefit from the use of FES but patient selection is likely multifactorial (i.e. motivation, fatigue, dosage) and likely not just related to disability level. Finding an exercise that people will invest in is really the key. Both interventions require further investigation, over longer periods of time.

Table 5.1 Change in outcomes measures from compared to MDC in other patient populations

Participant ID	PDDS	6MWT[a]	6MWT[b]	Gait Speed[a] (T2FW)	Gait Speed[b] (T2FW)	TUG[a]	TUG[b]	5XSST[a]	5XSST[b]	MFIS Total % change
Cycling 01	4	89.76*	22.5%	-0.16	-10.9%	0.98	13.2%	-0.49	5.4%	65%*
Cycling 02	6	-39.01	-19.3%	-0.11	-14.4%	3.92	22.6%	1.36	-8.3%	46%*
Cycling 03	3	-91.44	-27.1	-0.04	-3.1%	1.5	16.3%	-1.18	8.4%	12%
Cycling 04	4	72.24*	15.5%	0.51*	32.5%*	-0.92	-9.5%	-3.03*	25.1%	-29%
Cycling 05	3	147.52*	45.7%	0.03	1.9%	0.43	5.5%	-0.9	8.2%	75%*
Cycling 06	3	69.49*	20.8%	0.12*	9.4%	-1.5	-15.4%	-3.34*	29.4%	-13%
Cycling 07	3	17.68	3.48%	-0.01	-0.83%	0.11	1.6%	-2.28	28.1%	14%
FES 01	3	33.83	12.0%	0.06	6.2%	-2.72	-20.6%	-1.64	15.4%	-8%
FES 02	4	80.77*	14.6%	0.11*	5.7%	-0.69	-11.6%	-0.95	10.5%	41%*
FES 03	3	36.88*	10.1%	0.14*	9.7%	-1.8	-16.8%	-1.87	12.9%	11%
FES 04	5	3.96	2.75%	-0.01	-0.6%	-1.87	-7.7%	-3.37*	18.6%	51%*
FES 05	3	-15.24	-3.2%	-0.07	-4.0%	-0.33	-3.5%	-3.4*	21.1%	12%
FES 06	4	35.66	8.45%	0.02	1.7%	-0.63	-6.6%	-5.88*	46.2%	6%
FES 07	4	19.51	7.7%	0.16*	20.0%*	-4.32*	-23.7%*	-2.55*	13.3%	26%*
MDC										
		Chronic Stroke = 36.6m, Older Adult = 50m[182]	Chronic Stroke = 13% change[183]	Older Adult = 0.1m/s[182]	MS = > 20% change[135]	Chronic Stroke = 2.9 sec or 23% change[183]	MS = 23-24% change[141]	Older Adult = 2.5sec[184]		MS = 19.3% change[158]

Abbreviations: FES = Functional Electrical Stimulation, 6MWT = 6 Minute Walk Test, T25FW = Times 25-Foot Walk, TUG = Timed up and go, 5XSST =5 times sit to stand, MFIS = Modified fatigue impact scale

* Participant change score met MDC

a = Change in score from post to pre-intervention

b = percent change

Recommendations for Future Study

Design of a future research study should consider a larger sample with a sex distribution that is similar to the natural epidemiology of the disease. A more homogeneous sample of individuals based on disability level, especially walking speed and distance, may have produced more useful results. In addition, further research is needed across all disability levels for longer time periods in order to draw conclusions regarding patient selection, dosage, and long-term outcomes. Although eight weeks is commonly a long enough time period to see training effects, it is likely that a longer training period would have shown greater improvements. Ratchford et al[36] found strong compliance over a 6 month period of home-based FES cycling. Future studies in the home environment would be beneficial for this population since one of the goals of FES cycling for this population is to perform this exercise as part of a healthy lifestyle and not for a short training period. A home-based training program would allow PWMS to train at their convenience and consult with a therapist, as needed, if they required guidance regarding treatment.

Continued use of the following outcome measures are recommended: an aerobic capacity measurement (6MWT with or without VO_2max testing), a gait speed measurement (T24FW or 10MWT), functional LE strength measurement (5XSST or 30-second chair stand), disease-specific QOL scale (MSQOL-54, Multiple Sclerosis Functional Composite (MSFC) or Multiple Sclerosis Quality of Life Inventory (MSQLI)) and a fatigue measure (MFIS or Fatigue Severity Scale) are recommended. All participants completed the training sessions and tolerated cycling three times per week, and all were able to complete the 45-minute interval training session on their first training day. This was

unexpected and was likely due to the short rest intervals provided, the participant's ability to select a comfortable cycling speed (minimum was 45 rpm), and the customized training protocol. All participants were given at least one day of rest in between training sessions. It is unknown if this rest is necessary since other training configurations were not explored.

Four subjects reached 80% of their submaximal test in 4 weeks and likely could have progressed further by either challenging them to cycle for longer periods, applying greater resistance, or increasing speeds, but continued progression was limited due to research protocol. Two participants who presented at higher disability levels (dependent on a walker for ambulation), may have benefited from smaller adjustments in resistance. For these individuals, resistance was progressed more slowly over the training period, and therefore both individuals did not reach their maximum allowable resistance (80% of maximum workload). Data needs to be further analyzed to examine how many of the participants achieved their target heart rate range during the study since not all participants achieved their target HR for long enough periods during each training session.

Voluntary contractions recruit muscle fibers in a specific pattern – small, less fatigable motor units (Type I), followed by larger, more fatigable motor units (Type IIa and IIb). In contrast, electrical stimulation recruits muscle fibers in a more non-selective and random manner.[105,185] The exact mechanism of how FES cycling may specifically benefit PWMS is unknown, and more research is warranted in this area. A possible hypothesis is that stimulation helps to strengthen the more fatigable muscle fibers (e.g. Type IIa) that may not be used in everyday life, due to either restrictions on mobility or

fatigue.

There is emerging evidence that FES training can improve oxidative muscle metabolism in people with moderate to severe MS,[178] but this concept needs to be further explored in the mild to moderate population. Possible future research questions include: Would a more intensive cycling protocol carryover over more to walking ability? Do participants need to cycle at higher speeds (i.e. intensities) in order to see changes in walking performance and QOL? Would a combination of cycling and overground training produce better walking outcomes?

Study Limitations

The study was limited to a sample of convenience based on location of the research lab. This sample method may have skewed the results to be less representative of the variety of PWMS living in the community. Those who volunteered for this study may have been more motivated to improve their health compared to those who did not volunteer. Participant attendance was excellent, and possibly due to the stipend participants received, which may have let to heightened exercise compliance that may not be maintained outside a research environment.

Due to the small sample size, interpretation of the findings is limited. The sample was not representative of the female to male ratio seen in the general MS population, and therefore is not an accurate representation of the population of people living with MS. Results can only be generalized to individuals who fit the inclusion/exclusion criteria. The PDDS range of 3.0 – 6.0 was chosen to recruit a more homogeneous sample, but there was still a large amount of variability among the participants. This range was selected to investigate individuals with mild to moderate disability level and the desire to look at an

intensive protocol. In addition, those with greater disability were more likely to have difficulty attending regular sessions outside of their home environment.

Data collection was limited to certain time periods due to lab space availability and the schedule of the PI. Most participants completed their training during the same time of day. All clinical outcome measure testing was performed during the same time of day. The PI collected all the clinical outcome measures and was not blinded to group assignment. In addition, study participants were not blinded to group assignment. Activity levels outside of the intervention were not monitored and may have impacted the results. Participants were instructed not to start any new activities and to inform the PI regarding any changes in medication.

The dosage of cycling may not have been intense enough to promote changes in the chosen clinical and self-report measures. Cycling for longer periods, greater than 3 times per week for 45 minutes, may be indicated for select individuals and warrants further investigation.

Summary

Exercise is known to be an effective means of maintaining and improving function in PWMS. Finding an exercise regime that is enjoyable, safe, and effective for PWMS is critical in prevention of the degenerative effects of the disease, and for maintaining overall wellness. This study is unique in that it addressed the efficacy of FES cycling versus Cycling Only for PWMS over an 8-week training period using an intensive customized progression protocol. The results of this pilot study support that exercise in the form of FES Cycling or Cycling Only is beneficial and helps to maintain and improve aerobic capacity, functional LE strength, and QOL in people with mild to moderate MS.

FES is well-tolerated in this population, and the addition of FES to cycling may impact muscle strength more than cycling without FES, but further investigation is warranted.

References

1. National MS Society. MS Prevalence. https://www.nationalmssociety.org/About-the-Society/MS-Prevalence. Accessed April 7, 2018.
2. Lublin, FD, Reingold SC. Defining the clinical course of multiple sclerosis: results of an international survey. *Neurology*. 1996:907-911.
3. Atkins, G, Amor, S, Fletcher, JM, Mills K. *The Biology of Multiple Sclerosis*. New York: Cambridge University Press; 2012.
4. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis : The 2013 revisions Defining the clinical course of multiple sclerosis The 2013 revisions. 2014:1-10.
5. International Classification of Functioning, Disability and Health (ICF). World Health Organization. http://www.who.int/classifications/icf/en/. Accessed March 31, 2018.
6. O'Sullivan SB. *Physical Rehabilitation*. (O'Sullivan, Susan B., Schmitz TJ, ed.). Philadelphia: F.A. Davis Company; 2007.
7. Stuifbergen AK, Blozis SA, Harrison TC, Becker HA. Exercise, functional limitations, and quality of life: a longitudinal study of persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2006;87(7):935-943.
8. Turner AP, Kivlahan DR, Haselkorn JK. Exercise and quality of life among people with multiple sclerosis: looking beyond physical functioning to mental health and participation in life. *Arch Phys Med Rehabil*. 2009;90(3):420-428.
9. Prakash RS, Snook EM, Erickson KI, et al. Cardiorespiratory fitness: A predictor of cortical plasticity in multiple sclerosis. *Neuroimage*. 2007;34(3):1238-1244.
10. Dalgas U, Stenager E, Jakobsen J, et al. Resistance training improves muscle strength and functional capacity in multiple sclerosis. *Neurology*. 2009;73(18):1478-1484.
11. Filipi ML, Kucera DL, Filipi EO, Ridpath AC, Leuschen MP. Improvement in strength following resistance training in MS patients despite varied disability levels. *NeuroRehabilitation*. 2011;28(4):373-382.
12. Rampello A, Franceschini M, Piepoli M, et al. Effect of aerobic training on walking capacity and maximal exercise tolerance in patients with multiple sclerosis: a randomized crossover controlled study. *Phys Ther*. 2007;87(5):545-555.
13. Castro-Sánchez AM, Matarán-Peñarrocha GA, Lara-Palomo I, Saavedra-Hernández M, Arroyo-Morales M, Moreno-Lorenzo C. Hydrotherapy for the treatment of pain in people with multiple sclerosis: a randomized controlled trial. *Evid Based Complement Alternat Med*. January 2012:1-8.
14. Oken BS, Kishiyama S, Zajdel D, et al. Randomized controlled trial of yoga and exercise in multiple sclerosis. *Neurology*. 2004;62(11):2058-2064.
15. Cakt BD, Nacir B, Genç H, et al. Cycling progressive resistance training for people with multiple sclerosis: a randomized controlled study. *Am J Phys Med Rehabil*. 2010;89(6):446-457.
16. Collett J, Dawes H, Meaney A, et al. Exercise for multiple sclerosis: a single-blind randomized trial comparing three exercise intensities. *Mult Scler*. 2011;17(5):594-603.
17. Wier LM, Hatcher MS, Triche EW, Lo AC. Effect of robot-assisted versus conventional body-weight-supported treadmill training on quality of life for people

with multiple sclerosis. *J Rehabil Res Dev*. 2011;48(4):483-492.
18. Lo AC, Triche EW. Improving gait in multiple sclerosis using robot-assisted, body weight supported treadmill training. *Neurorehabil Neural Repair*. 2008;22(6):661-671.
19. Robinson, Andrew J, Snyder-Mackler L. *Clinical Electrophysiology: Electrotherapy and Electrophysiologic Testing*. 3rd ed. Baltimore: Lippincott Williams & Wilkins; 2008.
20. Kralj AR, Bajd T. *Functional Electrical Stimulation: Standing and Walking after Spinal Cord Injury*. CRC Press; 1989.
21. Liberson W, Holmquest H, Scot D, Dow M. Functional electrotherapy: stimulation of the peroneal nerve synchronized with the swing phase of the gait of hemiplegic patients. *Arch Phys Med Rehabil*. 1961;42(2):101-105.
22. Peckham PH, Knutson JS. Functional electrical stimulation for neuromuscular applications. *Annu Rev Biomed Eng*. 2005;7:327-360.
23. Alon G, Conroy VM, Donner TW. Intensive training of subjects with chronic hemiparesis on a motorized cycle combined with functional electrical stimulation (FES): a feasibility and safety study. *Physiother Res Int*. 2011;16(2):81-91.
24. Aaron SE, VanDerwerker CJ, Embry AE, Newton JH, Lee SCK, Gregory CM. FES-Assisted Cycling Improves Aerobic Capacity and Locomotor Function Post-CVA. *Med Sci Sport Exerc*. 2017:401-406.
25. Ferrante S, Pedrocchi A, Ferrigno G, Molteni F. Cycling induced by functional electrical stimulation improves the muscular strength and the motor control of individuals with post-acute stroke. *Eur J Phys Rehabil Med*. 2008;44(2):159-167.
26. Scremin AM, Kurta L, Gentili A, et al. Increasing muscle mass in spinal cord injured persons with a functional electrical stimulation exercise program. *Arch Phys Med Rehabil*. 1999;80(12):1531-1536.
27. Janssen TW, Beltman JM, Elich P, et al. Effects of electric stimulation-assisted cycling training in people with chronic stroke. *Arch Phys Med Rehabil*. 2008;89(3):463-469.
28. Chen S-C, Lai C-H, Chan WP, Huang M-H, Tsai H-W, Chen J-JJ. Increases in bone mineral density after functional electrical stimulation cycling exercises in spinal cord injured patients. *Disabil Rehabil*. 2005;27(22):1337-1341.
29. Frotzler A, Coupaud S, Perret C, et al. High-volume FES-cycling partially reverses bone loss in people with chronic spinal cord injury. *Bone*. 2008;43(1):169-176.
30. Fornusek C, Davis GM, Baek I. Stimulation of shank muscles during functional electrical stimulation cycling increases ankle excursion in individuals with spinal cord injury. *Arch Phys Med Rehabil*. 2012;93(11):1930-1936.
31. Yeh C-Y, Tsai K-H, Su F-C, Lo H-C. Effect of a bout of leg cycling with electrical stimulation on reduction of hypertonia in patients with stroke. *Arch Phys Med Rehabil*. 2010;91(11):1731-1736.
32. Chilibeck PD, Jeon J, Weiss C, Bell G, Burnham R. Histochemical changes in muscle of individuals with spinal cord injury following functional electrical stimulated exercise training. *Spinal Cord*. 1999;37(4):264-268.
33. Chang YJ, Hsu MJ, Chen SM, Lin CH, Wong AM. Decreased central fatigue in multiple sclerosis patients after 8 weeks of surface functional electrical stimulation. *J Rehabil Res Dev*. 2011;48(5):555-564.

34. Barrett CL, Mann GE, Taylor PN, Strike P. A randomized trial to investigate the effects of functional electrical stimulation and therapeutic exercise on walking performance for people with multiple sclerosis. *Mult Scler*. 2009;15(4):493-504.
35. Broekmans T, Roelants M, Feys P, et al. Effects of long-term resistance training and simultaneous electro-stimulation on muscle strength and functional mobility in multiple sclerosis. *Mult Scler*. 2011;17(4):468-477.
36. Ratchford JN, Shore W, Hammond ER, et al. A pilot study of functional electrical stimulation cycling in progressive multiple sclerosis. *NeuroRehabilitation*. 2010;27(2):121-128.
37. Krause P, Szecsi J, Straube A. FES cycling reduces spastic muscle tone in a patient with multiple sclerosis. *NeuroRehabilitation*. 2007;22:335-337.
38. Backus D, Burdett B, Hawkins L, Manella C, McCully KK, Sweatman M. Pilot study of outcomes after functional electrical stimulation cycle training in individuals with multiple sclerosis who are nonambulatory. *Int J MS Care*. 2016:1537-2073-36.
39. Khan F, Turner-Stokes L, Ng L. Multidisciplinary rehabilitation for adults with multiple sclerosis. *Cochrane database Syst Rev*. 2007;18(2):1-61.
40. Szecsi J, Schlick C, Schiller M, Pöllmann W, Koenig N, Straube A. Functional electrical stimulation-assisted cycling of patients with multiple sclerosis: biomechanical and functional outcome-a pilot study. *J Rehabil Med*. 2009;41(8):674-680.
41. Fornusek C, Hoang P. Neuromuscular electrical stimulation cycling exercise for persons with advanced multiple sclerosis. *J Rehabil Med*. 2014;46(7):698-702.
42. Hammond ER, Recio AC, Sadowsky CL, Becker D. Functional electrical stimulation as a component of activity-based restorative therapy may preserve function in persons with multiple sclerosis. *J Spinal Cord Med*. 2014;0(0):1-8.
43. Ambrosini E, Ferrante S, Pedrocchi A, Ferrigno G, Molteni F. Cycling induced by electrical stimulation improves motor recovery in postacute hemiparetic patients: a randomized controlled trial. *Stroke*. 2011;42(4):1068-1073.
44. Hooker SP, Figoni SF, Glaser RM, Rodgers MM, Ezenwa BN, Faghri PD. Physiologic responses to prolonged electrically stimulated leg-cycle exercise in the spinal cord injured. *Arch Phys Med Rehabil*. 1990;71(11):863-869.
45. Kleim JA, Jones TA. Principles of experience-dependent neural plasticity: implications for rehabilitation after brain damage. *J Speech, Lang Hear Res*. 2008;51:S225-S239.
46. White LJ, Castellano V. Exercise and brain health--implications for multiple sclerosis: Part 1--neuronal growth factors. *Sport Med*. 2008;38(2):91-100.
47. Zeller D, aufm Kampe K, Biller A, et al. Rapid-onset central motor plasticity in multiple sclerosis. *Neurology*. 2010;74(9):728-735.
48. Zehr EP. Neural control of rhythmic human movement: the common core hypothesis. *Exerc Sport Sci Rev*. 2005;33(1):54-60.
49. Kileff J, Ashburn A. A pilot study of the effect of aerobic exercise on people with moderate disability multiple sclerosis. *Clin Rehabil*. 2005;19(2):165-169.
50. Petajan JH, Gappmaier E, White AT, Spencer MK, Mino L, Hicks RW. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol*. 1996;39(4):432-441.
51. Dalgas U, Stenager E, Jakobsen J, Petersen T, Overgaard K, Ingemann-Hansen T. Muscle fiber size increases following resistance training in multiple sclerosis. *Mult*

Scler. 2010;16(11):1367-1376.
52. Dalgas U, Ingemann-Hansen T, Stenager E. Physical exercise and MS recommendations. *Int MS J*. 2009;16(1):5-11.
53. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444-1452.
54. Sabapathy NM, Minahan CL, Turner GT, Broadley SA. Comparing endurance- and resistance-exercise training in people with multiple sclerosis: a randomized pilot study. *Clin Rehabil*. 2011;25(1):14-24.
55. Dalgas U, Stenager E, Ingemann-Hansen T. Multiple sclerosis and physical exercise: recommendations for the application of resistance-, endurance- and combined training. *Mult Scler*. 2008;14(1):35-53.
56. Stroud N, Minahan C, Sabapathy S. The perceived benefits and barriers to exercise participation in persons with multiple sclerosis. *Disabil Rehabil*. 2009;31(26):2216-2222.
57. Johnston TE, Smith BT, Oladeji O, Betz RR, Lauer RT. Outcomes of a home cycling program using functional electrical stimulation or passive motion for children with spinal cord injury: a case series. *J Spinal Cord Med*. 2008;31(2):215-221.
58. Johnston TE, Wainwright SF. Cycling with functional electrical stimulation in an adult with spastic diplegic cerebral palsy. *Phys Ther*. 2011;91(6):970-982.
59. Naci H, Fleurence R, Birt J, Duhig A. Economic burden of multiple sclerosis: a systematic review of the literature. *Pharmacoeconomics*. 2010;28(5):363-379.
60. Multiple Sclerosis Council for Clinical Practice Guidelines. *Fatigue and Multiple Sclerosis: Evidence-Based Management Strategies for Fatigue in Multiple Sclerosis*. Washington D.C: Paralyzed Veterans of America; 1998.
61. Bonafede MM, Johnson BH, Wenten M, Watson C. Treatment patterns in disease-modifying therapy for patients with multiple sclerosis in the United States. *Clin Ther*. 2013;35(10):1501-1512.
62. Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. *Lancet Neurol*. 2010;9(12):1182-1199.
63. Matsuda PN, Shumway-Cook A, Bamer AM, Johnson SL, Amtmann D, Kraft GH. Falls in multiple sclerosis. *PM&R*. 2011;3(7):624-632.
64. Sosnoff JJ, Socie MJ, Boes MK, et al. Mobility, balance and falls in persons with multiple sclerosis. *PLoS One*. 2011;6(11):e28021-e28021.
65. Sosnoff JJ, Sandroff BM, Motl RW. Quantifying gait abnormalities in persons with multiple sclerosis with minimal disability. *Gait Posture*. 2012;36(1):154-156.
66. Benedetti MG, Piperno R, Simoncini L, Bonato P, Tonini A, Giannini S. Gait abnormalities in minimally impaired multiple sclerosis patients. *Mult Scler*. 1999;5(5):363-368.
67. Remelius JG, Jones SL, House JD, et al. Gait impairments in persons with multiple sclerosis across preferred and fixed walking speeds. *Arch Phys Med Rehabil*. 2012;93(9):1637-1642.
68. Freal, JE, Kraft, GH, Coryell J. Symptomatic fatigue in multiple sclerosis. *Arch Phys Med Rehabil*. 1984;65:135-138.
69. MacAllister WS, Krupp LB. Multiple sclerosis-related fatigue. *Phys Med Rehabil Clin N Am*. 2005;16(2):483-502.

70. Amato MP, Ponziani G, Rossi F, Liedl CL, Stefanile C, Rossi L. Quality of life in multiple sclerosis: the impact of depression, fatigue and disability. *Mult Scler*. 2001;7(5):340-344.
71. Mostert S, Kesselring J. Effects of a short-term exercise training program on aerobic fitness, fatigue, health perception and activity level of subjects with multiple sclerosis. *Mult Scler*. 2002;8(2):161-168.
72. Cavanaugh JT, Gappmaier VO, Dibble LE, Gappmaier E. Ambulatory activity in individuals with multiple sclerosis. *J Neurol Phys Ther*. 2011;35(1):26-33.
73. Stroud NM, Minahan CL. The impact of regular physical activity on fatigue, depression and quality of life in persons with multiple sclerosis. *Health Qual Life Outcomes*. 2009;7:68.
74. Hayes HA, Gappmaier E, LaStayo PC. Effects of high-intensity resistance training on strength, mobility, balance, and fatigue in individuals with multiple sclerosis: a randomized controlled trial. *J Neurol Phys Ther*. 2011;35(1):2-10.
75. Dalgas U, Stenager E, Jakobsen J, et al. Fatigue, mood and quality of life improve in MS patients after progressive resistance training. *Mult Scler*. 2010;16(4):480-490.
76. Motl RW, McAuley E, Snook EM, Gliottoni RC. Physical activity and quality of life in multiple sclerosis: intermediary roles of disability, fatigue, mood, pain, self-efficacy and social support. *Psychol Health Med*. 2009;14(1):111-124.
77. Page C Le, Ferry A, Rieu M, et al. Effect of muscular exercise on chronic relapsing experimental autoimmune encephalomyelitis. *J Appl Physiol*. 1994;77:2341-2347.
78. Gold SM, Schulz K-H, Hartmann S, et al. Basal serum levels and reactivity of nerve growth factor and brain-derived neurotrophic factor to standardized acute exercise in multiple sclerosis and controls. *J Neuroimmunol*. 2003;138(1-2):99-105.
79. Wens I, Keytsman C, Deckx N, Cools N, Dalgas U, Eijnde BO. Brain derived neurotrophic factor in multiple sclerosis: Effect of 24 weeks endurance and resistance training. *Eur J Neurol*. 2016;23(6):1028-1035.
80. Schulz K-H, Gold SM, Witte J, et al. Impact of aerobic training on immune-endocrine parameters, neurotrophic factors, quality of life and coordinative function in multiple sclerosis. *J Neurol Sci*. 2004;225(1-2):11-18.
81. White, L J, Dressendrofer R. Exericse and multiple sclerosis. *Sport Med*. 2004;34(15):1077-1100.
82. Ponichtera-Mulcare, J A, Mathews, T, Barret, P J, Gupta SC. Change in aerobic fitness of patients with multiple sclerosis during a 6-month training program. *Res Sport Med*. 1997;7(3-4):265-272.
83. Rodgers MM, Mulcare J a, King DL, Mathews T, Gupta SC, Glaser RM. Gait characteristics of individuals with multiple sclerosis before and after a 6-month aerobic training program. *J Rehabil Res Dev*. 1999;36(3):183-188.
84. Schapiro, RT, Petajan, JH, Kosich, D, Molk, B, Feeney J. Role of cardiovascular fitness in multiple sclerosis: a pilot study. *J Neuro Rehab*. 1988;2:43-49.
85. Gutierrez GM, Chow JW, Tillman MD, McCoy SC, Castellano V, White LJ. Resistance training improves gait kinematics in persons with multiple sclerosis. *Arch Phys Med Rehabil*. 2005;86(9):1824-1829.
86. Harvey L, Jones R. The Effect of Weighted Leg Raises on Quadriceps Strength, EMG Parameters and Functional Activities in People with Multiple Sclerosis. *Physiotherapy*. 1999;85(3):154-161.

87. White LJ, McCoy SC, Castellano V, et al. Resistance training improves strength and functional capacity in persons with multiple sclerosis. *Mult Scler*. 2004;10(6):668-674.
88. Taylor NF, Dodd KJ, Prasad D, Denisenko S. Progressive resistance exercise for people with multiple sclerosis. *Disabil Rehabil*. 2006;28(18):1119-1126.
89. Doucet BM, Lam A, Griffin L. Neuromuscular electrical stimulation for skeletal muscle function. *Yale J Biol Med*. 2012;85(2):201-215.
90. Glaser R. Physiologic aspects of spinal cord injury and functional neuromuscular stimulation. *Cent Nerv Syst Trauma*. 1986;3(1):49-62.
91. Dolbow DR, Gorgey AS, Ketchum JM, Moore JR, Hackett L a, Gater DR. Exercise adherence during home-based functional electrical stimulation cycling by individuals with spinal cord injury. *Am J Phys Med Rehabil*. 2012;91(11):922-930.
92. Dolbow DR, Gorgey AS, Moore JR, Gater DR. Report of practicability of a 6-month home-based functional electrical stimulation cycling program in an individual with tetraplegia. *J Spinal Cord Med*. 2012;35(3):182-186.
93. Duffell LD, Donaldson N de N, Perkins TA, et al. Long-term intensive electrically stimulated cycling by spinal cord-injured people: effect on muscle properties and their relation to power output. *Muscle Nerve*. 2008;38(4):1304-1311.
94. Reichenfelser W, Hackl H, Hufgard J, Kastner J, Gstaltner K, Gföhler M. Monitoring of spasticity and functional ability in individuals with incomplete spinal cord injury with a functional electrical stimulation cycling system. *J Rehabil Med*. 2012;44(5):444-449.
95. Hasnan N, Ektas N, Tanhoffer AIP, et al. Exercise responses during functional electrical stimulation cycling in individuals with spinal cord injury. *Med Sci Sports Exerc*. 2013;45(6):1131-1138.
96. Faghri, PD, Glaser, RM, Figoni S. Functional electrical stimulation leg cycle ergometer exercise: training effects on cardiorespiratory responses of spinal cord injured subjects at rest and during submaximal exercise. *Arch Phys Med Rehabil*. 1992;73(11):1085-1093.
97. Griffin L, Decker MJ, Hwang JY, et al. Functional electrical stimulation cycling improves body composition, metabolic and neural factors in persons with spinal cord injury. *J Electromyogr Kinesiol*. 2009;19(4):614-622.
98. Lai C-H, Chang WH-S, Chan WP, et al. Effects of functional electrical stimulation cycling exercise on bone mineral density loss in the early stages of spinal cord injury. *J Rehabil Med*. 2010;42(2):150-154.
99. Bauer P, Krewer C, Golaszewski S, Koenig E, Müller F. Functional electrical stimulation-assisted active cycling - Therapeutic effects in patients with hemiparesis from 7 days to 6 months after stroke: A randomized controlled pilot study. *Arch Phys Med Rehabil*. 2015;96(2):188-196.
100. Newman MA, Dawes H, van den Berg M, Wade DT, Burridge J, Izadi H. Can aerobic treadmill training reduce the effort of walking and fatigue in people with multiple sclerosis: a pilot study. *Mult Scler*. 2007;13(1):113-119.
101. Szecsi J, Götz S, Pöllmann W, Straube A. Force-pain relationship in functional magnetic and electrical stimulation of subjects with paresis and preserved sensation. *Clin Neurophysiol*. 2010;121(9):1589-1597.
102. Hammond ER, Recio AC, Sadowsky CL, Becker D. Functional electrical stimulation

as a component of activity-based restorative therapy may preserve function in persons with multiple sclerosis. *J Spinal Cord Med*. 2014;0(0):1-8.
103. Eser PC, Donaldson N de N, Knecht H, Stüssi E. Influence of different stimulation frequencies on power output and fatigue during FES-cycling in recently injured SCI people. *IEEE Trans Neural Syst Rehabil Eng*. 2003;11(3):236-240.
104. Paul L, Rafferty D, Young S, Miller L, Mattison P, McFadyen A. The effect of functional electrical stimulation on the physiological cost of gait in people with multiple sclerosis. *Mult Scler*. 2008;14(7):954-961.
105. Jubeau M, Gondin J, Martin A, Sartorio A, Maffiuletti NA. Random motor unit activation by electrostimulation. *Int J Sports Med*. 2007;28(11):901-904.
106. Hunt KJ, Hosmann D, Grob M, Saengsuwan J. Metabolic efficiency of volitional and electrically stimulated cycling in able-bodied subjects. *Med Eng Phys*. 2013;35(7):919-925.
107. Hunt KJ, Fang J, Saengsuwan J, Grob M, Laubacher M. On the efficiency of FES cycling: a framework and systematic review. *Technol Health Care*. 2012;20(5):395-422.
108. Kjaer, M, Perko, G, Secher, NH, Boushel, R, Beyer, N, Pollack, S, Horn, A, Fernandes, A, Mohr, T, Lewis S. Cardiovascular and ventilatory responses to electrically induced cycling with complete epidural anaesthesia in humans. *Acta Physiol Scand*. 1994;151:199-207.
109. *Restorative Therapies Clinician Guide*. Baltimore: Restorative Therapies; 2011.
110. Nasreddine Z. The Montreal Cognitive Assessment. http://www.mocatest.org/default.asp.
111. Cohen RA, Kessler HR, Fischer M. The Extended Disability Status Scale (EDSS) as a predictor of impairments of functional activities of daily living in multiple sclerosis. *J Neurol Sci*. 1993;115(2):132-135.
112. Hobart J, Freeman J, Thompson A. Kurtzke scales revisited: the application of psychometric methods to clinical intuition. *Brain*. 2000;123:1027-1040.
113. Patti F, Ciancio MR, Cacopardo M, et al. Effects of a short outpatient rehabilitation treatment on disability of multiple sclerosis patients--a randomised controlled trial. *J Neurol*. 2003;250(7):861-866.
114. Pilutti L a, Dlugonski D, Sandroff BM, et al. Gait and six-minute walk performance in persons with multiple sclerosis. *J Neurol Sci*. 2013;334(1-2):72-76.
115. Finkelstein J, Lapshin O, Castro H, Cha E, Provance PG. Home-based physical telerehabilitation in patients with multiple sclerosis: a pilot study. *J Rehabil Res Dev*. 2008;45(9):1361-1373.
116. Learmonth YC, Motl RW, Sandroff BM, Pula JH, Cadavid D. Validation of patient determined disease steps (PDDS) scale scores in persons with multiple sclerosis. *BMC Neurol*. 2013;13:37-44.
117. Hohol MJ, Orav EJ, Weiner HL. Disease steps in multiple sclerosis: a longitudinal study comparing Disease Steps and EDSS to evaluate disease progression. *Mult Scler*. 1999;5(5):349-354.
118. Hohol MJ, Orav E, Weiner HL. Disease Steps in multiple sclerosis : a simple approach to evaluate disease progression. *Neurology*. 1995;45:251-255.
119. North American Research Consortium on Multiple Sclerosis. Patient Determined Disease Steps. www.narcoms.org/pdds.

120. Alzheimer's Association. Research consent for cognitively impaired adults: recommendations for institutional review boards and investigatiors. *Alzheimer Dis Assoc Disord*. 2004;18(3):171-175.
121. Nasreddine Z, Phillips N, Bedirian V, et al. The Montreal Cognitive Assessment, MoCA: A Brief Screening Tool for Mild Cognitive Impairment. *JAGS*. 2005;53(4):695-699.
122. Cumming TB, Bernhardt J, Linden T. The montreal cognitive assessment: short cognitive evaluation in a large stroke trial. *Stroke*. 2011;42(9):2642-2644.
123. Dagenais E, Rouleau I, Demers M, et al. Value of the MoCA test as a screening instrument in multiple sclerosis. *Can J Neurol Sci*. 2013;40(3):410-415.
124. Godin, G, Shepard R. A simple method to assess exercise behavior in the community. *Can J Appl Sport Sci*. 1985;10(3):141-146.
125. Potter K, Allen D, Bennett S, et al. Multiple sclerosis outcome measures taskforce compendium of instructions for outcome measures. http://www.neuropt.org/docs/ms-edge-documents/ms-edge-compendium-of-instructions.pdf?sfvrsn=4. Published 2010. Accessed February 5, 2016.
126. Potter K, Allen D, Bennett S, et al. *MS EDGE Outcome Measures for Research*.; 2012.
127. Cattaneo D, Regola A, Meotti M. Validity of six balance disorders scales in persons with multiple sclerosis. *Disabil Rehabil*. 2006;28(12):789-795.
128. Nilsagård Y, Lundholm C, Denison E, Gunnarsson L-G. Predicting accidental falls in people with multiple sclerosis -- a longitudinal study. *Clin Rehabil*. 2009;23(3):259-269.
129. Goldman MD, Marrie RA, Cohen JA. Evaluation of the six-minute walk in multiple sclerosis subjects and healthy controls. *Mult Scler*. 2008;14(3):383-390.
130. Fry DK, Pfalzer LA. Reliability of Four Functional Tests and Rating of Perceived Exertion in Persons with Multiple Sclerosis. *Physiother canada*. 2006;58(3):212-220.
131. Fritz S, Lusardi M. White paper: "walking speed: the sixth vital sign". *J Geriatr Phys Ther*. 2009;32(2):46-49.
132. Gijbels D, Dalgas U, Romberg A, et al. Which walking capacity tests to use in multiple sclerosis? A multicentre study providing the basis for a core set. *Mult Scler*. 2012;18(3):364-371.
133. Bethoux F, Bennett S. Evaluating Walking in Patients with Multiple Sclerosis. *Int J MS Care*. 2011;13(1):4-14.
134. Fischer JS, Rudick R a., Cutter GR, Reingold SC. The Multiple Sclerosis Functional Composite measure (MSFC): an integrated approach to MS clinical outcome assessment. *Mult Scler*. 1999;5(4):244-250.
135. Hobart J, Blight AR, Goodman A, Lynn F, Putzki N. Timed 25-Foot Walk meaningful in MS. *Neurology*. 2013;80(16):1509-1517.
136. Goldman MD, Motl RW, Scagnelli J, Pula JH, Sosnoff JJ, Cadavid D. Clinically meaningful performance benchmarks in MS: timed 25-foot walk and the real world. *Neurology*. 2013;81(21):1856-1863.
137. Coleman CI, Sobieraj DM, Marinucci LN. Minimally important clinical difference of the Timed 25-Foot Walk Test: results from a randomized controlled trial in patients with multiple sclerosis. *Curr Med Res Opin*. 2012;28(1):49-56.
138. Kaufman M, Moyer D, Norton J. The significant change for the Timed 25-Foot Walk

in the Multiple Sclerosis Functional Composite. *Mult Scler*. 2000;6(3):286-291.
139. Uitdehaag BMJ, Adèr HJ, Kalkers NF, et al. Quantitative functional measures in MS: what is a reliable change? *Neurology*. 2002;58(4):1294-1296.
140. Herman T, Giladi N, Hausdorff JM. Properties of the "timed up and go" test: more than meets the eye. *Gerontology*. 2011;57(3):203-210.
141. Nilsagard Y, Lundholm C, Gunnarsson L-G, Dcnison E. Clinical relevance using timed walk tests and "timed up and go" testing in persons with multiple sclerosis. *Physiother Res Int*. 2007;12(2):105-114.
142. Csuka, M, McCarty D. Simple method for measurement of lower extremity muscle strength. *Am J Med*. 1985;78:77-81.
143. Bohannon RW, Bubela DJ, Magasi SR, Wang Y. Sit-to-stand test : Performance and determinants across the age-span. *Isokinet Exerc Sci*. 2010;18:235-240.
144. Duncan RP, Leddy AL, Earhart GM, Rp AD, Al L, Five EGM. Five Times Sit-to-Stand Test Performance in Parkinson's Disease. *Arch Phys Med Rehabil*. 2011;92(9):1431-1436.
145. Bohannon RW, Shove ME, Barreca SR, Masters LM. Five-repetition sit-to-stand test performance by community-dwelling adults : A preliminary investigation of times , determinants , and relationship with self-reported physical performance. *Isokinet Exerc Sci*. 2007;15:77-81.
146. Goldberg A. The five-times-sit-to-stand-test (FTSST), the short version of the activities-specific balance confidence (ABC) scale, and fear of falling predict step execution time (SET) in older adults. *Arch Gerontol Geriatr*. 2012;54(3):434-438.
147. Spain RI, St George RJ, Salarian A, et al. Body-worn motion sensors detect balance and gait deficits in people with multiple sclerosis who have normal walking speed. *Gait Posture*. 2012;35(4):573-578.
148. BTS G-Walk: a new approach to walking analysis. BTS Bioengineering. http://www.btsbioengineering.com/wp-content/uploads/2014/07/BTSWP_G-WALK-0514UK.pdf.
149. Hobart JC, Riazi A, Lamping DL, Fitzpatrick R, Thompson AJ. Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12). *Neurology*. 2003;60(1):31-36.
150. Motl RW, Snook EM. Confirmation and extension of the validity of the Multiple Sclerosis Walking Scale-12 (MSWS-12). *J Neurol Sci*. 2008;268(1-2):69-73.
151. Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. 2nd ed. New York: Lawrene Erlbaum Associates; 1988.
152. Weikert M, Suh Y, Lane A, et al. Accelerometry is associated with walking mobility, not physical activity, in persons with multiple sclerosis. *Med Eng Phys*. October 2011.
153. Motl RW, Dlugonski D, Suh Y, et al. Multiple Sclerosis Walking Scale-12 and oxygen cost of walking. *Gait Posture*. 2010;31(4):506-510.
154. Riazi A, Thompson AJ, Hobart JC. Self-efficacy predicts self-reported health status in multiple sclerosis. *Mult Scler*. 2004;10(1):61-66.
155. Fisk JD, Ritvo PG, Ross L, Haase DA, Marrie TJ, Schlech WF. Measuring the Fatigue Impact of Fatigue : Initial Validation Measuring the Functional Impact Scale. 2014;18(Suppl 1):S79-83.
156. Amtmann D, Bamer AM, Noonan V, Lang N, Kim J, Cook KF. Comparison of the

psychometric properties of two fatigue scales in multiple sclerosis. *Rehabil Psychol*. 2012;57(2):159-166.
157. Kos D, Kerckhofs E, Carrea I, Verza R, Ramos M, Jansa J. Evaluation of the Modified Fatigue Impact Scale in four different European countries. *Mult Scler*. 2005;11(1):76-80.
158. Rietberg MB, Van Wegen EEH, Kwakkel G. Measuring fatigue in patients with multiple sclerosis: reproducibility, responsiveness and concurrent validity of three Dutch self-report questionnaires. *Disabil Rehabil*. 2010;32(22):1870-1876.
159. Pilutti LA, Lelli DA, Paulseth JE, et al. Effects of 12 weeks of supported treadmill training on functional ability and quality of life in progressive multiple sclerosis: a pilot study. *Arch Phys Med Rehabil*. 2011;92(1):31-36.
160. Vickrey BG, Hays RD, Harooni R, Myers LW, Ellison GW. A health-related quality of life measure for multiple sclerosis. *Qual Life Res*. 1995;4(3):187-206.
161. Paul L, Coote S, Crosbie J, et al. Core outcome measures for exercise studies in people with multiple sclerosis: recommendations from a multidisciplinary consensus meeting. *Mult Scler*. March 2014.
162. Giordano A, Pucci E, Naldi P, et al. Responsiveness of patient reported outcome measures in multiple sclerosis relapses: the REMS study. *J Neurol Neurosurg Psychiatry*. 2009;80(9):1023-1028.
163. Powell L, Myers A. The Activities-specific Balance Confidence (ABC) Scale. *J Gerontol A Biol Sci Med Sci*. 1995;50A(1):M28-34.
164. Dibble LE, Lopez-Lennon C, Lake W, Hoffmeister C, Gappmaier E. Utility of disease-specific measures and clinical balance tests in prediction of falls in persons with multiple sclerosis. *J Neurol Phys Ther*. 2013;37(3):99-104.
165. Cattaneo D, Jonsdottir J, Repetti S. Reliability of four scales on balance disorders in persons with multiple sclerosis. *Disabil Rehabil*. 2007;29(24):1920-1925.
166. Durstine, JL, Moorre, GE, Painter, PL, Roberts S, ed. *ACSM'S Exercise Management for Persons with Chronic Diseases and Disablities*. 3rd ed. Champaign, IL: Human Kinetics; 2009.
167. *ACSM's Guidelines for Exercise Testing and Prescription*. 9th ed. Wolters Kluwer/Lippincott Williams & Wilkins Health; 2014.
168. Gappmaier E. The submaximal clinical exercise tolerance test (SXTT) to establish safe exercise prescription parameters for patients with chronic disease and disability. *Cardiopulm Phys Ther J*. 2012;23(2):19-29.
169. Jackson, K, Mulcare J. Multiple Sclerosis. In: Durstine, JL, Moore, GE, Paitner, PL, Roberts S, ed. *ACSM's Exercise Management for Persons with Chronic Diseases and Disabilites*. 3rd ed. Champaign, IL: Human Kinetics; 2009:321-326.
170. Cnaan A, Laird N, Slasor P. Using the general linear mixed model to analyse unbalanced repeated measures and longitudinal data. *Stat Med*. 1997;16:2349-2380.
171. Chapter 15 Mixed Models: a flexible approach to correlated data. CMU Statistics. http://www.stat.cmu.edu/~hseltman/309/Book/chapter15.pdf. Accessed November 5, 2017.
172. Martin CL, Phillips B a, Kilpatrick TJ, et al. Gait and balance impairment in early multiple sclerosis in the absence of clinical disability. *Mult Scler*. 2006;12(5):620-628.

173. Ferrante S, Ambrosini E, Ravelli P, et al. A biofeedback cycling training to improve locomotion: A case series study based on gait pattern classification of 153 chronic stroke patients. *J Neuroeng Rehabil*. 2011;8(1).
174. Lee MJ, Kilbreath SL, Singh MF, et al. Comparison of effect of aerobic cycle training and progressive resistance training on walking ability after stroke: A randomized sham exercise-controlled study. *J Am Geriatr Soc*. 2008;56(6):976-985. doi:10.1111/j.1532-5415.2008.01707.x.
175. McCarthy EK, Horvat MA, Holtsberg PA, Wisenbaker JWM. Repeated chair stands as a measure of lower limb strength in sexagenarian women. *J Gerontol Med Sci*. 2004;59A(11):1207-1212.
176. Mazzoleni S, Stampacchia G, Gerini A, Tombini T, Carrozza MC. FES-cycling training in spinal cord injured patients. *Conf Proc . Annu Int Conf IEEE Eng Med Biol Soc IEEE Eng Med Biol Soc Annu Conf*. 2013;2013:5339-5341.
177. Baumstarck K, Boyer L, Boucekine M, Michel P, Pelletier J, Auquier P. Measuring the Quality of Life in Patients with Multiple Sclerosis in Clinical Practice: A Necessary Challenge. *Mult Scler Int*. 2013;2013:1-8.
178. Reynolds MA, McCully K, Burdett B, Manella C, Hawkins L, Backus D. Pilot study: Evaluation of the effect of functional electrical stimulation cycling on muscle metabolism in nonambulatory people with multiple sclerosis. *Arch Phys Med Rehabil*. 2015;96(4):627-632.
179. Braley TJ, Chervin RD. Fatigue in multiple sclerosis: Mechanisms, evaluation, and treatment. *Sleep*. 2010;33(8):1061-1067. doi:10.1093/sleep/33.8.1061.
180. Portney LG, Watkins MP. *Foundations of Clinical Research: Applications to Practice*. 3rd ed. Upper Saddle River, NJ: Pearson/Prentice Hall; 2015.
181. Charron S, McKay KA, Tremlett H. Physical activity and disability outcomes in multiple sclerosis: A systematic review (2011–2016). *Mult Scler Relat Disord*. 2018;20(October 2017):169-177.
182. Perera S, Mody SH, Woodman RC, Studenski SA. Meaningful change and responsiveness in common physical performance measures in older adults. *J Am Geriatr Soc*. 2006;54(5):743-749.
183. Flansbjer UB, Holmbäck AM, Downham D, Patten C, Lexell J. Reliability of gait performance tests in men and women with hemiparesis after stroke. *J Rehabil Med*. 2005;37(2):75-82.
184. Goldberg A, Chavis M, Watkins J, Wilson T. The five-times-sit-to-stand test: validity, reliability and detectable change in older females. *Aging Clin Exp Res*. 2012;24(4):339-344.
185. Gregory CM, Bickel CS. Recruitment Patterns in Human. *Phys Ther*. 2005;85(4):358-364.

Appendix A: Recruitment Flyer and Letter

Research Volunteers Needed

People at least 18 years of age with a diagnosis of multiple sclerosis are needed to participate in a cycling study. Individuals must be ambulatory and have transportation.

Participation involves eight weeks of training on an exercise bike with or without electrodes stimulating muscles in both legs. It also involves 2 sessions of functional testing that includes walking and other daily activities. All session will be supervised by a licensed physical therapist. No significant risks are associated with this study. You may experience benefits consistent with exercising on a stationary bike.

Duration: 8 weeks, 3 times per week for 1 ½ hour sessions and 2 testing session approximately 2 hours in length.
Location: Stony Brook University, The RRAMP Lab, Development Drive, Building 17, Suite 120, Stony Brook, NY 11794-6018

Compensation: Participants will receive up to $250 for participation in the study.

This study has been approved by the IRB at Stony Brook University.

For more information, or if you are interested in participating, please contact Lori Hochman, **(631)444-1193**, lori.hochman@stonybrook.edu

Stony Brook University

Dear Healthcare Practitioner,

I am writing to tell you about a research study being conducted at Stony Brook University. I am a faculty member in the Doctor of Physical Therapy Program and I am working toward completing my PhD through Nova Southeastern University in Ft. Lauderdale, Fl. This research study is being conducted as part of my doctoral dissertation. This study has been approved by the IRB at Stony Brook University and Nova Southeastern University.

The study involves an exercise-training program using a Functional Electrical Stimulation (FES) cycle. Participants who meet the inclusion/exclusion criteria will train for 3 times per week for 8 weeks and will receive either 8 weeks of FES cycling OR 8 weeks of cycling without FES. Participants will not a stipend to participate in the study.

I am looking for participants who are at least 18 years of age who have a definite diagnosis of multiple sclerosis (MS) and whose symptoms interfere with their walking ability and who can walk at least 25 feet with or without an assistive device.

Participants will not be able to take part in the study if they have:

a. Cognitive deficits that would limit their ability to participate in cycling
b. Received physical therapy within the last 4 weeks prior to the study
c. Inadequate range of motion at the hip and knee for cycling
d. Significant spasticity in the lower extremities that may interfere with the cycling motion
e. Received immunosuppressive or steroid therapy within the past 4 weeks
f. History of an acute exacerbation of their MS symptoms 4 weeks prior to the study
g. Coronary artery disease
h. History of congestive heart failure
i. Uncontrolled hypertension
j. History of epilepsy or history of seizures
k. Cardiac demand pacemaker
l. Implanted defibrillator
m. Unhealed fractures in the lower extremities
n. Pressure sores or open wounds in the area of treatment (buttocks, thighs, shin, and calves)
o. Pregnant or trying to conceive.

If you know a person who meets the above criteria and is interested in participating, please ask them to contact me at lori.hochman@stonybrook.edu or 631-444-1193.

Sincerely,

Lori Hochman, PT, MS, NCS

Lori Hochman, PT, MS, NCS
Clinical Assistant Professor
Physical Therapy Program

Appendix B: Phone Screening Form and PDDS

Phone Screening Form Today's date/time: _____
Person screening: _____
Participant Name: _____ Age: _____
Sex: ☐M ☐ F Cell #: _____ Other #: _____(Home or Work)
E-mail (primary): _____(secondary): _____

---

1. **Do you have a diagnosis of MS?**
   ☐ Yes ☐No

2. **Do you utilize an assistive device?**

   ☐ Yes ☐No
   If yes, what device and how often?
   _____

3. **Do you have any other neurological pathologies (e.g. stroke, h/o Guillian-Barre, TBI)?**

   ☐ Yes ☐No
   _____

4. **Have you received PT within the last 4 weeks or are you currently receiving PT?**

   ☐ Yes ☐No
   If yes, what was the date of your last session?
   _____

5. **Have you had an exacerbation within the last 4 weeks?**

   ☐ Yes ☐No
   If yes, what was the date of your last exacerbation? Did you receive steroids or other medications during this time?

---

6. **Do you have a history or currently have of any of the following medical issues?**

   Congestive Heart Failure: ☐ Yes ☐No
   Heart Disease: ☐ Yes ☐No
   High Blood Pressure: ☐ Yes ☐No
   Epilepsy: ☐ Yes ☐No

Seizures: ☐ Yes ☐No
Pacemaker: ☐ Yes ☐No
Defibrillator: ☐ Yes ☐No
Leg fractures: ☐ Yes ☐No
Wounds or sores on legs: ☐ Yes ☐No

7. **Are you pregnant or trying to conceive? (women only)**

   ☐ Yes ☐No

8. **Do you have, or have you had any recent musculoskeletal injuries that would affect your ability to pedal a seated stationary bicycle? (i.e., muscle strains, sprains)**

   ☐ Yes ☐No
   If yes, explain the circumstances in which this occurred.
   _____

9. **This study will take approximately 8 weeks and attendance is required three times per week for approx. 1-11/2 hours. In addition, there will be three sessions for data collection, one at the beginning, one at the end of the 8 weeks and one-month after training. Are you able to consistently attend sessions?**

   ☐ Yes ☐No

Initial Visit Scheduled: _____

Patient Determined Disease Steps (PDDS)

Please read choices listed below and choose the one that best describes your own situation. **This scale focuses mainly on how well you walk.** You might not find a description that reflects your condition exactly, but please mark the one category that describes your situation the closest.

☐**0 Normal:** I have some mild symptoms, mostly sensory due to MS but they do not limit my activity. If I do have an attack, I return to normal when the attack has passed.

☐**1 Mild Disability:** I have some noticeable symptoms from my MS but they are minor and have only a small effect on my lifestyle.

☐**2 Moderate Disability:** I don't have any limitations in my walking ability. However, I do have significant problems due to MS that limit daily activities in other ways.

☐**3 Gait Disability:** MS does interfere with my activities, especially my walking. I can work a full day, but athletic or physically demanding activities are more difficult that they used to be. I usually don't need a cane or other assistance to walk, but I might need some assistance during an attack.

☐**4 Early Cane:** I use a cane or a single crutch or some other form of support (such as touching a wall or leaning on someone's arm) for walking all the time or part of the time, especially when walking outside. I think I can walk 25 feet in 20 seconds without a cane or crutch. I always need some assistance (cane or crutch) if I want to walk as far as 3 blocks.

☐**5 Late Cane:** To be able to walk 25 feet, I have to have a cane, crutch or someone to hold onto. I can get around the house or other buildings by holding onto furniture or touching the walls for support. I may use a scooter or wheelchair if I want to go greater distances.

☐**6 Bilateral Support:** To be able to walk as far as 25 feet I must have 2 canes or crutches or a walker. I may use a scooter or wheelchair for longer distances.

☐**7 Wheelchair/Scooter:** My main form of mobility is a wheelchair. I may be able to stand and/or take one or two steps, but I can't walk 25 feet, even with crutches or a walker.

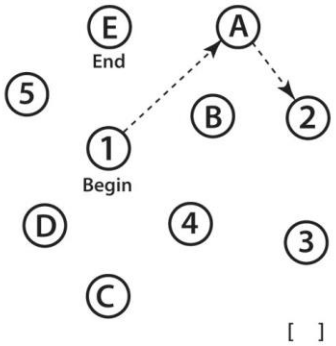
☐**8 Bedridden:** Unable to sit in a wheelchair for more than one hour.

Appendix C: Montreal Cognitive Assessment, Administration and Scoring

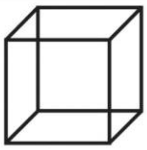
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube



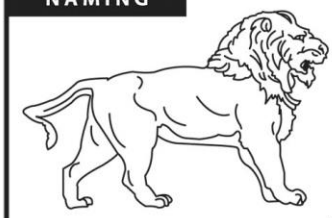
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

NAMING



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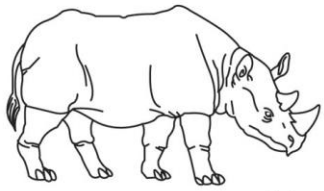

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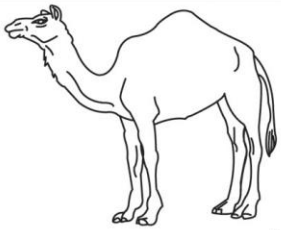


[ ]

__/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2
__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B
__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**
__/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ]
__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)
__/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler
__/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City
__/6

© Z.Nasreddine MD www.mocatest.org Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

Montreal Cognitive Assessment
(MoCA)
Administration and Scoring Instructions

The Montreal Cognitive Assessment (MoCA) was designed as a rapid screening instrument for mild cognitive dysfunction. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuoconstructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal.

1. Alternating Trail Making:

Administration: The examiner instructs the subject: "Please draw a line, going from a number to a letter in ascending order. Begin here [point to (1)] and draw a line from 1 then to A then to 2 and so on. End here [point to (E)]."

Scoring: Allocate one point if the subject successfully draws the following pattern: 1 −A- 2- B- 3- C- 4- D- 5- E, without drawing any lines that cross. Any error that is not immediately self-corrected earns a score of 0.

2. Visuoconstructional Skills (Cube):

Administration: The examiner gives the following instructions, pointing to the cube: “Copy this drawing as accurately as you can, in the space below”.

Scoring: One point is allocated for a correctly executed drawing.
• Drawing must be three-dimensional
• All lines are drawn
• No line is added
• Lines are relatively parallel and their length is similar (rectangular prisms are accepted)
A point is not assigned if any of the above-criteria are not met.

3. Visuoconstructional Skills (Clock):

Administration: Indicate the right third of the space and give the following instructions: “Draw a clock. Put in all the numbers and set the time to 10 past 11”.

Scoring: One point is allocated for each of the following three criteria:
• Contour (1 pt.): the clock face must be a circle with only minor distortion acceptable (e.g., slight imperfection on closing the circle);
• Numbers (1 pt.): all clock numbers must be present with no additional numbers; numbers must be in the correct order and placed in the approximate quadrants on the clock face; Roman numerals are acceptable; numbers can be placed outside the circle contour;
• Hands (1 pt.): there must be two hands jointly indicating the correct time; the hour hand must be clearly shorter than the minute hand; hands must be centered within the clock face with their junction close to the clock center.
A point is not assigned for a given element if any of the above-criteria are not met.

4. Naming:

Administration: Beginning on the left, point to each figure and say: “Tell me the name of this animal”.
Scoring: One point each is given for the following responses: (1) lion (2) rhinoceros or rhino (3) camel or dromedary.

5. Memory:

Administration: The examiner reads a list of 5 words at a rate of one per second, giving the following instructions: “This is a memory test. I am going to read a list of words that you will have to remember now and later on. Listen carefully. When I am through, tell me as many words as you can remember. It doesn’t matter in what order you say them”. Mark a check in the allocated space for each word the subject produces on this first trial. When the subject indicates that (s)he has finished (has recalled all words), or can recall no more words, read the list a second time with the following instructions: “I am going to read the same

list for a second time. Try to remember and tell me as many words as you can, including words you said the first time." Put a check in the allocated space for each word the subject recalls after the second trial.
At the end of the second trial, inform the subject that (s)he will be asked to recall these words again by saying, "I will ask you to recall those words again at the end of the test."

Scoring: No points are given for Trials One and Two.

6. Attention:

Forward Digit Span:

Administration: Give the following instruction: "I am going to say some numbers and when I am through, repeat them to me exactly as I said them". Read the five number sequence at a rate of one digit per second.
Backward Digit Span: Administration: Give the following instruction: "Now I am going to say some more numbers, but when I am through you must repeat them to me in the backwards order." Read the three number sequence at a rate of one digit per second.

Scoring: Allocate one point for each sequence correctly repeated, (N.B.: the correct response for the backwards trial is 2-4-7).

Vigilance:
Administration: The examiner reads the list of letters at a rate of one per second, after giving the following instruction: "I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand".

Scoring: Give one point if there is zero to one errors (an error is a tap on a wrong letter or a failure to tap on letter A).

Serial 7s:
Administration: The examiner gives the following instruction: "Now, I will ask you to count by subtracting seven from 100, and then, keep subtracting seven from your answer until I tell you to stop." Give this instruction twice if necessary.

Scoring: This item is scored out of 3 points. Give no (0) points for no correct subtractions, 1 point for one correction subtraction, 2 points for two-to-three correct subtractions, and 3 points if the participant successfully makes four or five correct subtractions. Count each correct subtraction of 7 beginning at 100. Each subtraction is evaluated independently; that is, if the participant responds with an incorrect number but continues to correctly subtract 7 from it, give a point for each correct subtraction. For example, a participant may respond "92 – 85 – 78 – 71 – 64" where the "92" is incorrect, but all subsequent numbers are subtracted correctly. This is one error and the item would be given a score of 3.

7. Sentence repetition:

Administration: The examiner gives the following instructions: "I am going to read you a sentence. Repeat it after me, exactly as I say it [pause]: I only know that John is the one to help today." Following the response, say: "Now I am going to read you another sentence. Repeat it after me, exactly as I say it [pause]: The cat always hid under the couch when dogs were in the room."

Scoring: Allocate 1 point for each sentence correctly repeated. Repetition must be exact. Be alert for errors that are omissions (e.g., omitting "only", "always") and substitutions/additions (e.g., "John is the one who helped today;" substituting "hides" for "hid", altering plurals, etc.).

8. Verbal fluency:

Administration: The examiner gives the following instruction: "Tell me as many words as you can think of that begin with a certain letter of the alphabet that I will tell you in a moment. You can say any kind of word you want, except for proper nouns (like Bob or Boston), numbers, or words that begin with the same sound but have a different suffix, for example, love, lover, loving. I will tell you to stop after one minute. Are you ready? [Pause] Now, tell me as many words as you can think of that begin with the letter F. [time for 60 sec]. Stop."

Scoring: Allocate one point if the subject generates 11 words or more in 60 sec. Record the

subject's response in the bottom or side margins.

9. Abstraction:

Administration: The examiner asks the subject to explain what each pair of words has in common, starting with the example: "Tell me how an orange and a banana are alike". If the subject answers in a concrete manner, then say only one additional time: "Tell me another way in which those items are alike". If the subject does not give the appropriate response (fruit), say, "Yes, and they are also both fruit." Do not give any additional instructions or clarification. After the practice trial, say: "Now, tell me how a train and a bicycle are alike". Following the response, administer the second trial, saying: "Now tell me how a ruler and a watch are alike". Do not give any additional instructions or prompts.

Scoring: Only the last two item pairs are scored. Give 1 point to each item pair correctly answered. The following responses are acceptable:
Train-bicycle = means of transportation, means of travelling, you take trips in both;
Ruler-watch = measuring instruments, used to measure.
The following responses are not acceptable: Train-bicycle = they have wheels; Rulerwatch = they have numbers.

10. Delayed recall:

Administration: The examiner gives the following instruction: "I read some words to you earlier, which I asked you to remember. Tell me as many of those words as you can remember." Make a check mark (√) for each of the words correctly recalled spontaneously without any cues, in the allocated space.

Scoring: Allocate 1 point for each word recalled freely without any cues.

Optional: Following the delayed free recall trial, prompt the subject with the semantic category cue provided below for any word not recalled. Make a check mark (√) in the allocated space if the subject remembered the word with the help of a category or multiple-choice cue. Prompt all non-recalled words in this manner. If the subject does not recall the word after the category cue, give him/her a multiple choice trial, using the following example instruction, "Which of the following words do you think it was, NOSE, FACE, or HAND?"
Use the following category and/or multiple-choice cues for each word, when appropriate:
FACE: category cue: part of the body multiple choice: nose, face, hand
VELVET: category cue: type of fabric multiple choice: denim, cotton, velvet
CHURCH: category cue: type of building multiple choice: church, school, hospital
DAISY: category cue: type of flower multiple choice: rose, daisy, tulip
RED: category cue: a colour multiple choice: red, blue, green
Scoring: No points are allocated for words recalled with a cue. A cue is used for clinical information purposes only and can give the test interpreter additional information about the type of memory disorder. For memory deficits due to retrieval failures, performance can be improved with a cue. For memory deficits due to encoding failures, performance does not improve with a cue.

11. Orientation:

Administration: The examiner gives the following instructions: "Tell me the date today". If the subject does not give a complete answer, then prompt accordingly by saying: "Tell me the [year, month, exact date, and day of the week]." Then say: "Now, tell me the name of this place, and which city it is in."

Scoring: Give one point for each item correctly answered. The subject must tell the exact date and the exact place (name of hospital, clinic, office). No points are allocated if subject makes an error of one day for the day and date.

TOTAL SCORE: Sum all subscores listed on the right-hand side. Add one point for an individual who has 12 years or fewer of formal education, for a possible maximum of 30 points. A final total score of 26 and above is considered normal.

Appendix D: Demographic and Medical Questionnaire

Participant ID#: _____

PERSONAL INFORMATION:

Name: _____

Address: _____

Contact phone numbers: Home: _____

Cell phone: _____

Preferred method of communication: ☐Home ☐Cell ☐Text Message ☐Email

Family Physician and/or Primary Health Care Provider:

Doctor/Other _____ Phone _____

Address _____ City _____

Neurologist:

Name _____ Phone _____

Address _____ City _____

DEMOGRAPHICS:

Age: _____

Date of Birth: _____

Gender: ☐Male, ☐Female

Marital Status: ☐Married ☐Single ☐Divorced ☐Widowed

Education:

☐Grade School ☐Jr. High School ☐High School
☐College (2-4 years) ☐Graduate School

Occupation: _____

MS DIAGNOSIS:

Date of first diagnosis: _____

Age when first symptoms of MS occurred: _____

Do you know which category you currently fit in?

☐Relapsing Remitting

☐Secondary Progressive

☐Primary Progressive

☐Progressive Relapsing

MEDICATIONS:

Currently Prescribed Medications (include name, dosage, and frequency)

Name	Dosage	Frequency

List any self-prescribed medications, dietary supplements, or vitamins you are now taking: _____

_____

_____

Are you currently on any of the disease modifying drugs? (Copaxone, Rebif, Avonex, Betaseron)?

If yes, which ones:

_____

If not, have you ever been and which ones?

_____

SYMPTOM INFORMATION:

When was your last exacerbation?

_____

How many exacerbations have you had?

_____

How often do they occur?

_____

Which of the following MS symptoms have you experienced?

☐Fatigue	☐Depression
☐Numbness/Tingling	☐Cognitive Problems
☐Pain	☐Balance Problems
☐Visual Problems	☐Coordination Problems
☐Muscle Spasms/Spasticity	☐Gait Problems
☐Bladder Problems	☐Dizziness
☐Bowel Problems	☐Tremors
☐Sexual Dysfunction	☐Slurred Speech
☐Weakness	☐Heat Sensitivity

Other symptoms:

_____

Have you received Physical Therapy within the last 4 weeks?

☐ Yes, date of last session was: _____

☐ No

Present Medical History:

Check those questions to which your answer is yes (leave others blank).

- ☐ High Blood Pressure
- ☐ Heart attack, if so, how many years ago? _____
- ☐ Rheumatic Fever
- ☐ Heart murmur
- ☐ Congestive Heart Failure
- ☐ Diseases of the arteries
- ☐ Varicose veins
- ☐ Arthritis of legs or arms
- ☐ Diabetes or abnormal blood-sugar tests
- ☐ Phlebitis (inflammation of a vein)
- ☐ Dizziness or fainting spells
- ☐ Epilepsy or seizures
- ☐ Stroke
- ☐ Diphtheria
- ☐ Scarlet Fever
- ☐ Infectious mononucleosis
- ☐ Nervous or emotional problems
- ☐ Anemia
- ☐ Thyroid problems
- ☐ Pneumonia
- ☐ Bronchitis
- ☐ Asthma
- ☐ Abnormal chest X-ray
- ☐ Other lung disease
- ☐ Injuries to back, arms, legs or joint
- ☐ Broken bones
- ☐ Jaundice or gall bladder problems

Comments: _____
_____
_____
_____

Do you have a cardiac pacemaker or defibrillator? _____

Check the box next to ☐YES or ☐NO for each question.

Has a doctor ever said your blood pressure was too high? ☐YES, ☐NO
Do you ever have pain in your chest or heart? ☐YES, ☐NO
Are you often bothered by a thumping of the heart? ☐YES, ☐NO
Does your heart often race? ☐YES, ☐NO
Do you ever notice extra heartbeats or skipped beats? ☐YES, ☐NO
Are your ankles often badly swollen? ☐YES, ☐NO
Do cold hands or feet trouble you even in hot weather? ☐YES, ☐NO
Has a doctor ever said that you have or have had heart trouble, an abnormal electrocardiogram (ECG or EKG), heart attack or coronary? ☐YES, ☐NO
Do you suffer from frequent cramps in your legs? ☐YES, ☐NO
Do you often have difficulty breathing? ☐YES, ☐NO
Do you sometimes get out of breath when sitting still or sleeping? ☐YES, ☐NO
Has a doctor ever told you your cholesterol level was high? ☐YES, ☐NO

Comments: _____
_____

Do you now have or have you recently experienced:

- ☐ Chronic, recurrent or morning cough?
- ☐ Episode of coughing up blood?
- ☐ Increased anxiety or depression?
- ☐ Problems with recurrent fatigue, trouble sleeping or increased irritability?
- ☐ Migraine or recurrent headaches?
- ☐ Stiff or painful joints?
- ☐ Pain in your legs after walking short distances?
- ☐ Foot problems?
- ☐ Back problems?
- ☐ Stomach or intestinal problems, such as recurrent heartburn, ulcers, constipation or diarrhea?
- ☐ Significant vision or hearing problems?
- ☐ Significant unexplained weight loss?
- ☐ A deep vein thrombosis (blood clot)?
- ☐ A hernia that is causing symptoms?
- ☐ Foot or ankle sores that won't heal?
- ☐ Persistent pain or problems walking after you have fallen?

Comments: _____
_____

Women only, please answer the following. Do you have:

- ☐ Menstrual period problems?
- ☐ Significant childbirth - related problems?
- ☐ Urine loss when you cough, sneeze or laugh?

List any other medical or diagnostic test you have had in the past two years: _____
_____

List hospitalizations, including dates of and reasons for hospitalization: _____
_____

List any drug allergies: _____
_____

Familial Diseases

Do you have any biological relatives with the diagnosis of MS? How are they related to you?
_____
_____

If there is any other information you would like to share with us, please let us know. Signing this indicated the information you have given is accurate by your account.

Print Name: _____
Signature: _____
Date: _____

Appendix E: Physical Assessment

Participant ID#: _____

Evaluation

Strength and Range of Motion Assessment:

	Hip Flex.	Hip Abd	Hip Extension	Knee Flex.	Knee Extension	Ankle DF
Right LE						
PROM						
AROM						
Strength	**/5**	**/5**	**/5**	**/5**	**/5**	**/5**
Left LE						
PROM						
AROM						
Strength	**/5**	**/5**	**/5**	**/5**	**/5**	**/5**

KEY: AROM= Active Range of Motion, PROM= Passive Range of Motion, Flex= flexion, / = Extension, WNL= Within Normal Limits, WFL= Within Functional Limits.
Comments: _____

Does the subject have adequate him, knee, and ankle ROM for cycling?
☐**Yes** ☐**No**

Sensation:

	Light Touch	Proprioception
Right Leg	☐**Impaired** ☐**Intact** ☐**Absent**	☐**Impaired** ☐**Intact** ☐**Absent**
Left Leg	☐**Impaired** ☐**Intact** ☐**Absent**	☐**Impaired** ☐**Intact** ☐**Absent**

Comments:
_____

Muscle Tone:
Ankle Clonus: ☐Absent ☐Present R/L ☐Sustained ☐ Un-sustained: ___ beats

	Right	Left
Lower Extremity	☐**Normal** ☐**Hypertonic** ☐**Rigid** ☐**Hypotonic** ☐**Flaccid** ☐**Mixed**	☐**Normal** ☐**Hypertonic** ☐**Rigid** ☐**Hypotonic** ☐**Flaccid** ☐**Mixed**
Upper Extremity	☐**Normal** ☐**Hypertonic** ☐**Rigid** ☐**Hypotonic** ☐**Flaccid** ☐**Mixed**	☐**Normal** ☐**Hypertonic** ☐**Rigid** ☐**Hypotonic** ☐**Flaccid** ☐**Mixed**

Balance:

Sitting	
Supported	☐**Stable** ☐**Requires Assistance** _____
Unsupported	☐**Stable** ☐**Requires Assistance** _____
Dynamic	☐**Stable** ☐**Requires Assistance** _____

Standing	
Supported	☐**Stable** ☐**Requires Assistance** _____
Unsupported	☐**Stable** ☐**Requires Assistance** _____
Dynamic	☐**Stable** ☐**Requires Assistance** _____

Cardiopulmonary Status:

Vitals	HR	BP	Oxygen Saturation	RPE	Comments
Resting					
After gait evaluation					

Circulation: Edema? ☐Yes ☐No, Location: _____
Additional Information: _____

Functional Mobility: **KEY: <u>Levels of Assistance</u> Total A = Total Assistance, Max Maximal Assist, Mod A = Moderate Assistance, Min A = Minimal Assistance, CG = Contact Guard, CS = Close Supervision, S = Supervision,**
DS = Distant Supervision, Modified I = Modified Independent. I =Independent.
<u>Devices</u> WBQC = Wide Base Quad Cane, NBQC = Narrow Base Quad Cane, HC = Hemicane, SAC = Single Axis Cane

Bed Mobility and Transfers:

Activity	**Level of Assistance**
Overall bed mobility	
Sit ➔Stand	
Stand ➔ Sit	

Ambulation	
Device	
Distance	
Level of Assistance	
Gait Quality	

Appendix F: Research Consent Form

Committees on Research Involving Human Subjects
Established 1971

RESEARCH CONSENT FORM

Project Title: Effects of Functional Electrical Stimulation Cycling versus Cycling Only on Walking Performance and Quality of Life in Individuals with Multiple Sclerosis: A Pilot Study

Principal Investigator: Lori Hochman, PT, MS, NCS, Clinical Assistant Professor
Co-Investigators: Lisa Muratori, PT, PhD, Clinical Associate Professor
Department: Department of Physical Therapy

You are being asked to be a volunteer in a research study.

PURPOSE

The purpose of this study is:

- To study the effects of cycling with and without the use of electrical stimulation to the leg muscles on walking performance and quality of life in people with multiple sclerosis.
- 20 individuals will be enrolled in the study and will be randomly assigned to one of the two treatment groups.

PROCEDURES

If you decide to be in this study, your part will involve:

- You will begin with filling out questionnaires about your medical history and your ability to perform daily activities.
- You will then undergo a brief exam that will test your muscle strength, sensation, and movement.
- You will be randomly assigned to one of the treatment groups (cycling with electrical stimulation or cycling without stimulation).

Procedures for FES cycling group:

- Functional Electrical Stimulation (FES) passes a very low level of electrical current through peripheral nerves to stimulate muscles to contract. FES cycling creates a rhythmical lower leg cycling pattern.
- Five muscle groups will be stimulated during every session (buttocks, front of the thigh, back of the thigh, front of the lower leg, back of the lower leg). Stimulation will be adjusted to ensure comfort during cycling.
- You will be seated in an armchair during all intervention sessions.
- You will be permitted to take a break or stop cycling during intervention sessions.

Procedures for Cycling only group:

- If you are in the cycling-only group you will not receive electrical stimulation.
- You will be seated in an armchair during all intervention sessions.
- You will be permitted to take a break or stop cycling during intervention sessions.

Participation Requirements for both groups:

Visit #	Session Summary	Time
1	Screening (questionnaires) and Baseline testing (walking performance and functional leg strength measures)	2 hours
2-12	Cycling intervention	1.5 hour each
13	Outcome measure testing (walking performance and functional leg strength measures) followed by a cycling intervention session	2.5 hours
14-25	Cycling intervention	1.5 hour
26	Outcome Measure Testing (walking performance and functional leg strength)	1 hour
27	Post-intervention outcome measures (one month after visit #25)	1 hour
		Total Time: 41 hours

- Participation involves 8-10 consecutive weeks of training. Cycling interventions (visit 2-25) must be scheduled with at least one day in between (e.g. Monday, Wednesday, Friday). Sessions may take place on the weekend
- With your permission, we may videotape you during the cycling or outcome testing sessions.

RISKS / DISCOMFORTS

The following risks/discomforts may occur as a result of you being in this study:

If you are randomly selected to be in the FES cycling training group:

- You will feel a prickling sensation under the electrodes and most people tolerate this well. The setting of the stimulation will be increased according to a protocol and adjusted for comfort.
- You may also experience your muscles tensing up and relaxing while you are cycling. This is a normal reaction to electrical stimulation.
- You may have red areas on your skin after the electrical stimulation treatment. The red area would be under the electrodes where the current was being delivered. This red area should disappear after 15 minutes. Your skin will be monitored throughout the study.
- You may experience fatigue from exercise and this will be monitored throughout the study. This is a temporary exercise induced fatigue rather than the central fatigue that you may experience as part of MS.
- You may experience a temporary increase in leg spasms after using the cycle.

If you are randomly selected to be in the cycling only training group:

- You may experience fatigue from exercise and this will be monitored throughout the study. This is a temporary exercise induced fatigue rather than the central fatigue that you may experience as part of MS.
- You may experience an increase in leg spasms after using the cycle.

BENEFITS

There is no direct benefit expected as a result of you being in this study. You may experience benefit similar to exercising on a bike three days per week.

PAYMENT TO YOU

You will be paid a total of $250.00 for this study.
The payment schedule is as follows:

Timeline	Payment
After week 2	$55
After week 4	$55
After week 6	$55
After week 8	$55
After week 12	$30
Total:	$250

PAYMENT TO THE INSTITUTION

This project is funded, in part, by a grant from the New York Physical Therapy Association, to the Research Foundation of Stony Brook University, in support of the Investigators' work on this study.

CONFIDENTIALITY

Protecting Your Privacy in this Study

All information obtained in this study is strictly confidential unless disclosure is required by law. We will take steps to help make sure that all the information we get about you is kept private. Your name will not be used wherever possible. We will use a code instead. All the study data that we get from you will be kept locked up for a period of at least three (3) years. The code will be locked up too. If any papers and talks are given about this research, your name will not be used and your face will not be visible on video. All video recordings will also be kept locked up and stored in the Rehabilitation Research and Movement Performance (RRAMP) Laboratory.

We want to make sure that this study is being done correctly and that your rights and welfare are being protected. For this reason, we will share the data we get from you in this study with the study team, the sponsor of this study (New York Physical Therapy Association), Stony Brook University's Committee on Research Involving Human Subjects, applicable Institutional officials, and certain federal offices. However, if you tell us you are going to hurt yourself, hurt someone else, or if we believe the safety of a child is at risk, we will have to report this.

In a lawsuit, a judge can make us give him the information we collected about you.

While you are in this study you will need to provide us with data about your health. We will also get health data from the results of the tests you will have done in this study. You have a right to privacy but the data we get about your health in this study can be shared with the people referenced above (the study team, Stony Brook University's Committee on Research Involving Human Subjects, applicable institutional officials, and certain federal offices).

Your health data are shared to make sure the study is being done correctly, costs are charged correctly, and to make sure your rights and safety are protected. Not all of these people are required by law to protect your health data. They might share it with others without your permission.

Some of the health information we get from you in this study cannot be shared with you until the end of the study.

You have the right to stop allowing us to use or give out your health data. You can do this at any time by writing to Lori Hochman. If you do this, we will stop collecting any new

health data from you, except if we need to keep an eye on a bad side effect you were having in the study. We will use any data we collected before you wrote your letter. When you sign the consent form at the end, it means:

- That you have read this section.
- That you will allow the use and reporting of your health data as described above.
- If you are paid $600 or more a year as a research subject, your social security number will be reported to those in charge of taxes. You may have to pay taxes on this money.

Clinical Trial Registry

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

COSTS TO YOU

- You are responsible for transportation to and from the research lab.

ALTERNATIVES

- Your alternative to being in this study is to simply not participate.

IN CASE OF INJURY

If you are injured as a result of being in this study, please contact Lori Hochman, PT at 631-444-1193. The services of Stony Brook University Hospital will be open to you in case of such injury. However, you and/or your insurance company will be responsible for payment of any resulting treatment and/or hospital stay.

REMOVAL FROM STUDY

- You will be removed from the study if you fail to attend scheduled training sessions within the allotted time period.
- You will be removed from the study if you experience a worsening of symptoms.
- You will be removed from the study if you report that you are pregnant or trying to conceive.

YOUR RIGHTS AS A RESEARCH SUBJECT

- Your participation in this study is voluntary. You do not have to be in this study if you don't want to be.
- You have the right to change your mind and leave the study at any time without giving any reason, and without penalty.

- Any new information that may make you change your mind about being in this study will be given to you.
- You will get a signed and dated copy of this consent form to keep.
- You do not lose any of your legal rights by signing this consent form.

Video Recording

- This research project may include video recording during any outcome measure testing or cycling sessions for periods of minute or less. This video recording will be available to be seen by the researcher, Stony Brook University Committee on Research Involving Human Subjects, any granting agencies, my dissertation committee, physical therapists and physical therapy students. If this video is used in papers or talks, we will make sure your face is not visible. Video will be recorded on a password protected mobile device and then transferred to a password protected computer. Video will then be deleted from the mobile device. You can request not to be videotaped and this will not affect your eligibility or participation in the study.

☐ I give permission to be video recorded. Initials: _____ Date: _____

☐ I do not give permission to be video recorded. Initials: _____ Date: _____

QUESTIONS ABOUT THE STUDY OR YOUR RIGHTS AS A RESEARCH SUBJECT

- If you have any questions, concerns, or complaints about the study, you may contact [Lori Hochman, Investigator], at telephone # (631-444-1193).
- If you have any questions about your rights as a research subject or if you would like to obtain information or offer input, you may contact Ms. Judy Matuk, Committee on Research Involving Human Subjects, (631) 632-9036, OR by e-mail, judy.matuk@stonybrook.edu.
- Visit Stony Brook University's Community Outreach page, http://www.stonybrook.edu/research/orc/community.shtml for more information about participating in research, frequently asked questions, and an opportunity to provide feedback, comments, or ask questions related to your experience as a research subject.

If you sign below, it means that you have read (or have had read to you) the information given in this consent form, and you would like to be a volunteer in this study.

Subject Name (Printed)	Subject Signature	Date

Name of Person Obtaining Consent (Printed)	Signature of Person Obtaining Consent	Date

Appendix G: Procedure Manual

PROCEDURE MANUAL

Effects of Functional Electrical Stimulation Cycling versus Cycling Only on Walking Performance and Quality of Life in Individuals with Multiple Sclerosis: A Randomized, Clinical Pilot Study

Lori Hochman, PT, MS, NCS, PhD(c)

Procedures

A. Phone Screening

1. Potential participants will undergo a phone screening prior to their initial visit to see if they meet all the inclusion/exclusion criteria (Phone Screening and PPDS).
2. If they meet the initial criteria they will be asked to set-up an appointment to meet with the primary investigator at the RRAMP LAB for a 2-hour session.
3. Sent participants directions and tell them to wear comfortable shoes and a loose pair of shorts with an elastic waistband.

B. First Meeting/Baseline Session Overview

1. Administer MoCA (must score 22 or greater)
2. Participant completes the PDDS again (must score between 3.0 and 6.0)
3. Participant completes Demographic/History Form (PI reviews form for eligibility)
4. Review consent forms and give the participant an opportunity to bring it home if they would like. They can also choose to sign on the spot and continue with baseline measurements during this meeting.
5. If they sign consent during this first visit, they will then be randomized into either the FES Cycling group or the Cycling Only group before all evaluation and testing begins. Blocked randomization will be used, and 4 papers were put in a hat where 2 choices are FES and 2 are Cycling only. After the first 4 participants select all 4 choices will be returned to the hat. This will help ensure even groups by the end of the pilot study.
6. PI performs physical examination and completes examination form
7. Objective baseline measures will be obtained in the following order: 6MWT, T25W(2 trials), TUG, 5XSST.
8. Sub-Maximal Exercise Test on the cycle

9. FES group: Electrode set-up and baseline stimulation levels will be obtained; Cycling only group- no set-up during this meeting
10. Set-up training schedule
11. Subjective outcome measures (GLTQ, MFIS, MSQOL-54, 12 Item MSWS, ABC) will be given to participants at the end of the baseline session and they can either stay and fill them out in the lab or bring them home and bring them back completed before their first training session.

Outcome Measures

Selected outcome measures will be performed at the follow intervals (see table)

- baseline- within one-week prior to the first training session;
- mid-point of training- between 1-3 days after the 12th training session;
- post-training- between 1-3 days after the 24th training session, and
- one-month after the last training session.

Physical tests were administered in the following order for each participant

1. 6MWT*
2. T25W*
3. TUG*
4. 5STS (no GWALK)

*BTS G-Walk worn during measurement

Participants will be provided at least a **five-minute rest period between all physical tests**. Safety precautions during testing will include: a quiet area free of distractions, gait belt, guarding and assistance as needed.

Outcome Measure	Collection of Data
Godin Leisure-Time Exercise Questionnaire (GLTEQ)	• Baseline
12 Item Multiple Sclerosis Walking Scale (MSWS-12)	• Baseline • Post-training • 1 month after training
Modified Fatigue Impact Scale (MFIS)	• Baseline • Post-training • 1 month after training
Multiple Sclerosis Quality of Life Inventory (MSQOL 54)	• Baseline • Post-training • 1 month after training
Activities Specific Balance Scale (ABC)	• Baseline • Post-training • 1 month after training
Timed Up and Go (TUG)	• Baseline • Mid-point • Post-training • 1 month after training
Five Times Sit-to-Stand (5STS)	• Baseline • Mid-point • Post-training • 1 month after training
6 Minute Walk (6MWT)	• Baseline • Mid-point • Post-training • 1 month after training
Gait Speed Time 25-Foot Walk (T25FW)	• Baseline • Mid-point • Post-training • 1 month after training

BTS G-WALK SET-UP

Laptop

1. Double click on G-Studio Icon and allow it to open

G-Walk Sensor

- Make sure Bluetooth is enabled by clicking the Bluetooth Icon under the "Sensor Management"
- Make sure G-Walk sensor is charged (hover over battery icon to check %). If not charged, plug USB into computer and wire into the sensor.

Database Selection

1. Click “Database Management” tab at top
2. Click on icon that has the yellow folder (looks like a hard drive with a yellow folder on top on it). If you hover over it, it says “Select Database”
3. Select “FES Cycling” and click ok
4. You will see collect patients on the left

Software Set-up for a New Patient

1. Click on the New Patient Icon on the far left (Blue plus sign)
2. Under “Personal Data” tab- fill in the following fields
    - Surname/Last Name: “FES Cycling” or “Cycling” depending on group
    - First Name: 01, 02, 03
    - Weight- lbs.
    - Height-ft./inches
    - Gender:
    - Shoe size- US sizes (e.g. 7.5)
    - Leg Length
3. Under “Anthropometrics” tab- Enter height in inches of Greater trochanter to lateral malleolus of both the right and left legs
4. Click “Save” at the bottom of the screen

Set-up for Collection

1. Click on that patient (e.g. Cycling 01) on the left side and that will open their folder and you will see all of their data in the middle panel if they are a continuing patient. If they are new, it will be empty.
2. To start collection, click the “Walk” icon on the left when doing the 6MW. Before saving, record type 6 MWT= _____ft.
3. For T25 W, click the “Walk” icon on the left when doing the T25W. Before saving, type “T25FW= _____seconds.” Do two trials.
4. For the TUG, click on the “Timed Up and Go Icon”. Before saving, type, TUG= _____ seconds.
5. Do a Five Times Sit to stand but do not use the G-Walk for this, just a stopwatch.

Placement of Sensor

1. Place the sensor in the pouch. The port goes to the sky and serial # goes to the back on bare skin.
2. Belt goes at L5. Tighten belt so sensor does not move.

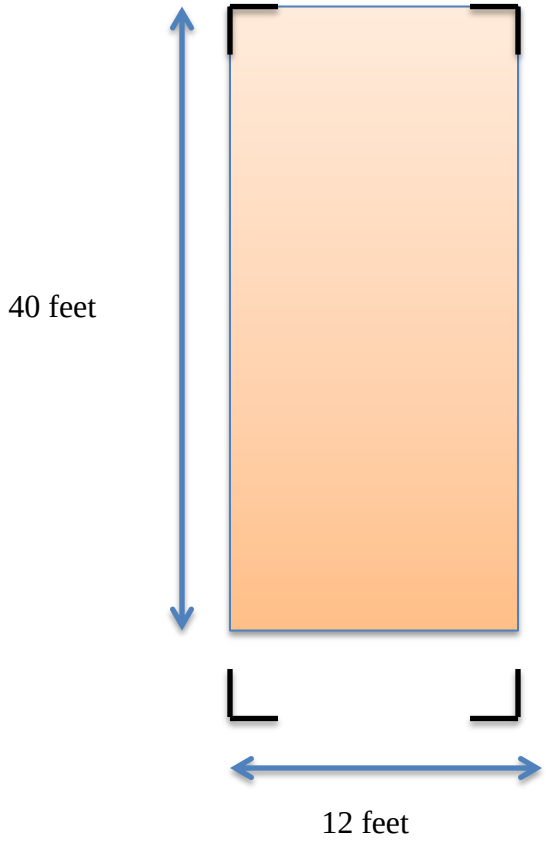
Data Collection

1. Click arrow next to START ON-LINE (to check if it is working). You should see 6 lines going across the screen.
2. Then click STOP STORAGE
3. When ready, click START ON-LINE again “START STORAGE” when you are ready to collect.
4. It will say “Waiting for Stabilization”
5. Then press “Stop Storage” when done collecting.

6. Then at the bottom of the screen click "(OK) Save"
7. Put notes in analysis screen. (e.g. 6MW- 2250 feet, 25FW- 5 seconds, TUG- 6 seconds)

TEST 1: 6MWT

Set-up: The testing will be an area of 40-foot straight walkway that will include 90 turns at each end.



The area has purple tape markers at the corners to mark the turn points. The total distance of the walking area is 104 feet. Laps will be counted and the distance after the start line will be measured with a measuring wheel after the test is complete.

Equipment:

- gait belt
- stop watch
- pulse oximeter
- rate of perceived exertion scale
- a chair that can be easily moved along the walking course
- sphygmomanometer

Participant Instructions:

"The object of this test is to walk as far and as fast as possible for 6 minutes with consideration for safety while you are walking. You will around the rectangle and turn at each corner. Six minutes is a long time to walk, so you will be exerting yourself. You should turn at each end corner of the rectangle and continue along the pathway. Now I'm going to show you."

(Investigator demonstrates)

"Are you ready to do that? I am going to use this stopwatch and this clipboard to keep track of time and the number of laps you complete. I will notify you of your time at 2 minutes and every minute after that. Remember that the object is to walk as far as and as fast as possible for 6 minutes, but don't run or jog. Start when you are ready."

When the timer shows 4 minutes: "Two minutes have passed, you have 4 minutes to go."

When the timer shows 3 minutes: "Three minutes have passed, you have three minutes to go."

When the timer shows 2 minutes: "Four minutes have passed, you have two minutes to go."

When the timer shows 1 minute: "Five minutes have passed, you only have one-minute left."

When the timer is 15 seconds from completion: "In a moment, I am going to tell you to stop. When I do, just stop where are and I will come to you."

The place where the person stopped will be marked and a chair will be brought over to them, so they can safely sit.

If the person stops walking during the test, the following phrase will be used:

"You are doing well. You should keep walking if you are able."

***If the person feels they cannot continue or the investigator feels they should no longer continue, a chair will be brought over to the person and the spot they stopped will be marked. ***

Reason for stopping and RPE will be recorded.

******GIVE PARTICIPANTS A MINIMUM OF A 5-MINUTE REST BEFORE STARTING THE NEXT TEST******

TEST 2: T25W

General Information:

Individuals can walk with or without an assistive device for 25 feet.

- If an assistive device is used it should be kept consistent and documented from trial to trial
- Two trials will be collected, and an average will be calculated
- The subject will wear a gait belt during this test.

Trial 1 and 2
Set the stopwatch at zero. The subject will be directed to the starting line that is clearly marked on the floor and will be asked to start 10 feet behind the line. The researcher will then point out where the course ends, and the subject will be given the following instructions.

"I'd like you to walk 25 feet as quickly as possible, but safely. Do not slow down until you have passed the finish line. Ready? Go."

Timing will begin when the lead foot is lifted and crosses the starting line. The examiner will walk along with the subject as he/she completes the task. Timing will stop when the lead foot crosses the finish line. The examiner will record the subject's walk time to within 0.1 second, rounding as needed. Round up to the next tenth if hundredth's place is> = .05, round down if hundredth's place is <.05 (e.g., 32.45" would round to 32.5" but 32.44"would round to 32.4"). Once the time is recorded, be sure to reset the stopwatch. Do two trials.

******GIVE PARTICIPANTS A MINIMUM OF A 5-MINUTE REST BEFORE STARTING THE NEXT TEST******

TEST 3: TUG

Equipment needed: The participant will sit on a standard armchair, placing his/her back against the chair and resting his/her arms chair's arms. Any assistive device used for walking will be nearby. Regular footwear and customary walking aids will be used. An iPhone stopwatch will be used to time the test (in seconds).

Set-up: A 3-meter (9.8 feet) walkway will be measured and marked. A standard height chair (seat height 17 inches, arm height 26 inches- use black cycling chair) will be placed at the beginning of the walkway.

Test: The participant walks to a line that is 3 meters (9.8 feet) away, turns around at the line, walk back to the chair, and sits down. The test ends when the participant's buttocks touch the seat. Participants will be instructed to use a comfortable and safe walking speed. One trial only.

Patient Instructions:
"Please sit in the chair and place your I back against the chair and rest your arms chair's arms. When I say go, walk at comfortable and safe walking speed. Walk to the line and turn at the line and then come back to the chair and sit down. Let me demonstrate for you first"

******GIVE PARTICIPANTS A MINIMUM OF A 5-MINUTE REST BEFORE STARTING THE NEXT TEST******

TEST 4: 5XSST

Equipment:

- Straight back chair with an 18 1/2" seat to floor height
- Stop watch (iPhone)

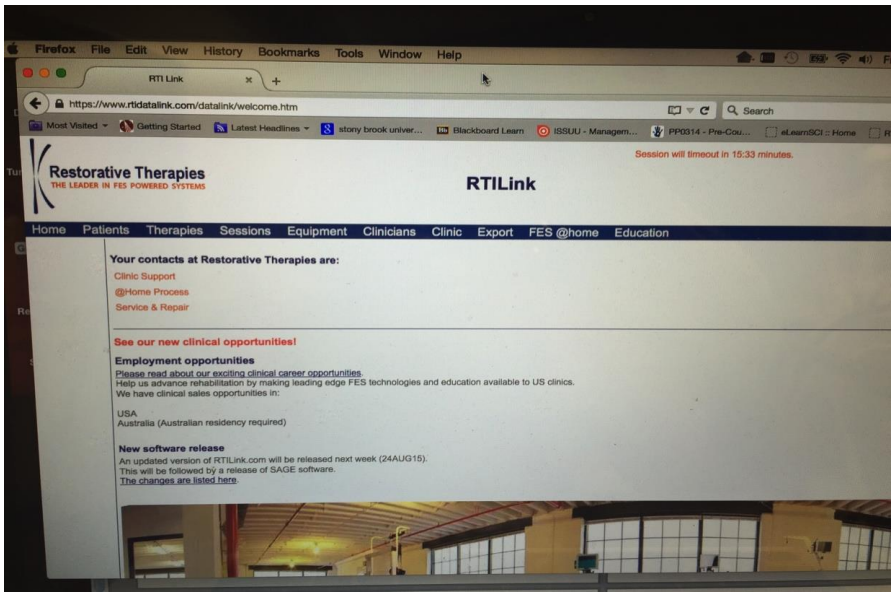
Instructions:
"Stand up and sit down as quickly as possible 5 times, keeping your arms folded across your chest." "Ready, go."

Measurement:
Start timing when the participant's buttocks leave the seat. Stop timing when the participant stands the 5th time. **One trial only.**

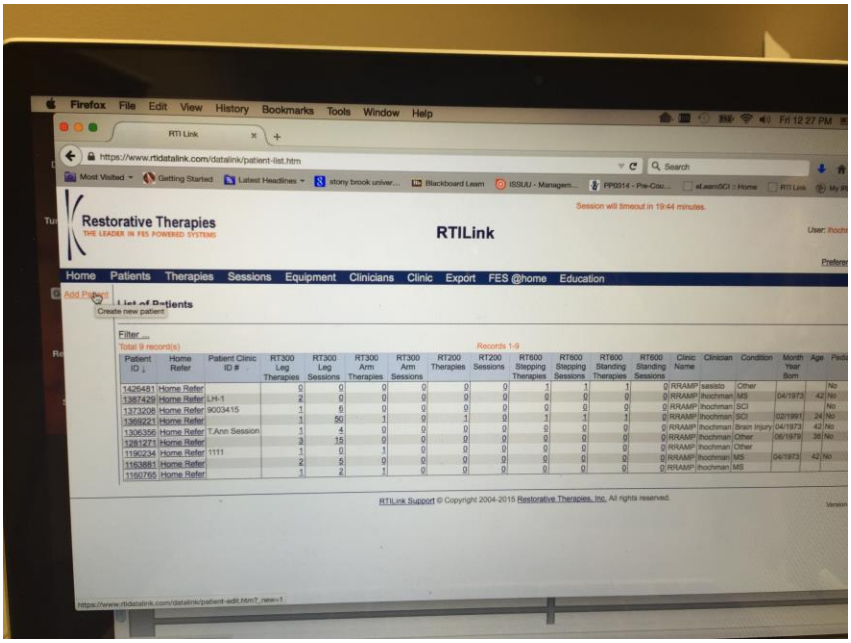
RTI Data Link Set-up

Basic demographic information (age, weight, and diagnosis) will be entered into Restorative Therapies Internet (RTI) Data Link and a random ID number will be generated, and subjects will choose their own 4-digit pin number. The participant number will be used as the participant ID number on all paperwork associated with the study.

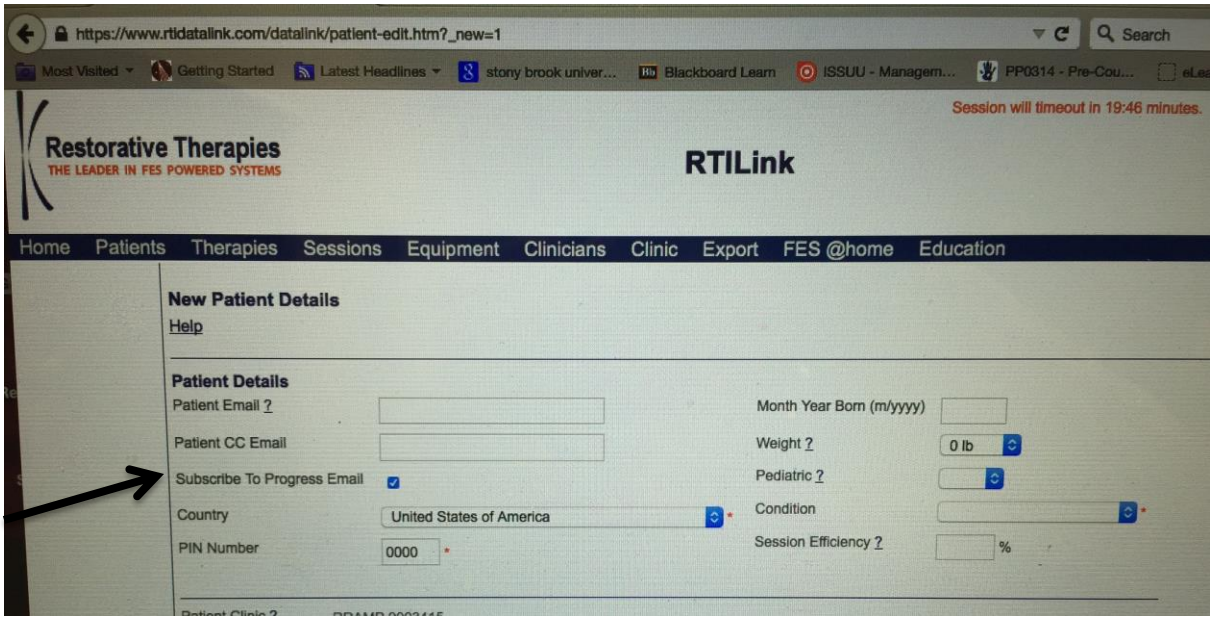
1. Go to www.rtidatalink.com
2. Put in username: _____, password: _____
3. Click "Log In"
4. Click on "Patients" at the top tool blue tool bar



5. Click on "Add Patient" located on the upper left-hand side

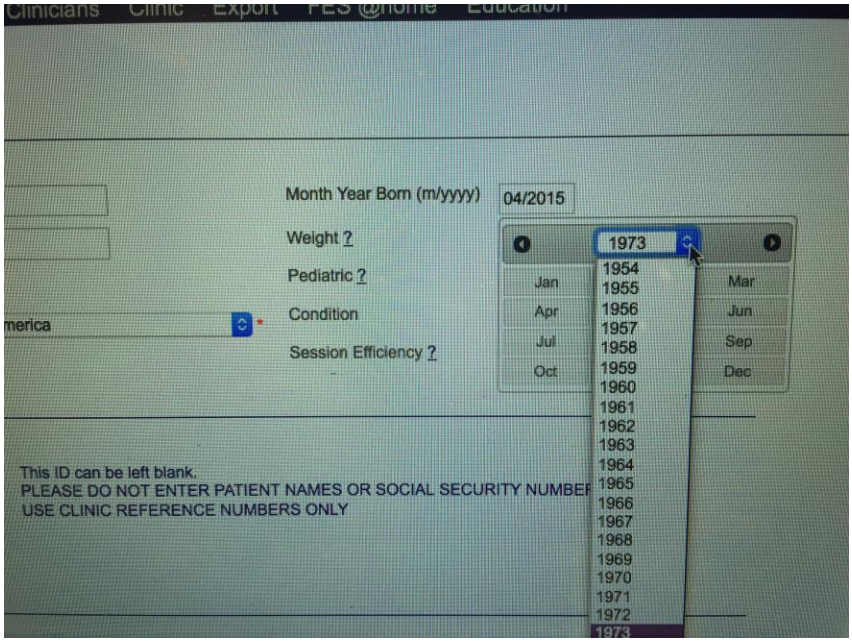


6. Enter the following information for each participant
    a. Patient email: _____
    b. Subscribe to progress email- **<u>UNCHECK BOX</u>** (patient should not receive progress reports during the study)



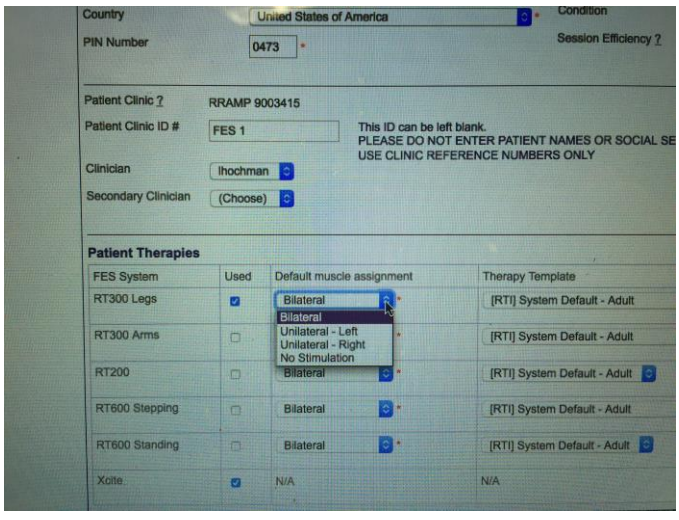
    c. Month and Year Born (month/year) (click on the month and scroll to the year and double click until the year appear in box). This generates the patients PIN Number which is the month and year of their birthday. (E.g.

April 1973, PIN will be 0473)

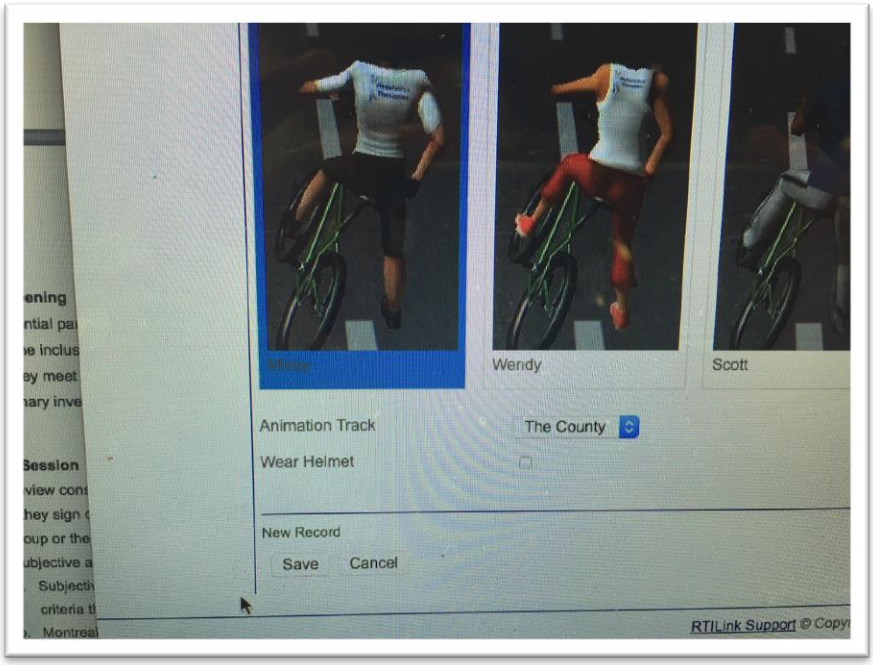


d. Enter weight in lbs. by scrolling down.
e. Condition- scroll down to "MS"
f. Patient Clinic ID# _____ (this will be generated by the system after you save)
g. Clinician: lhochman
h. Patient Therapies:

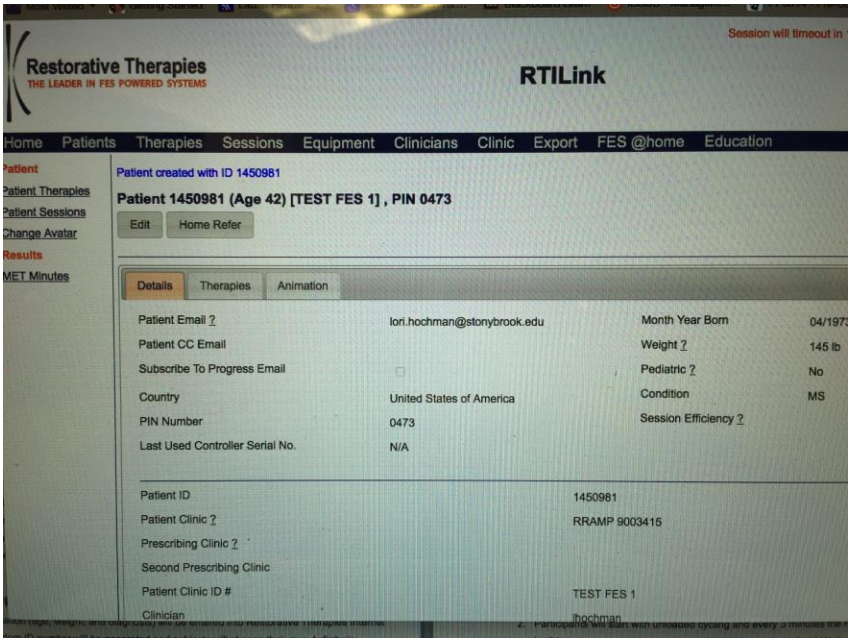
   Therapy Template- Select Bilateral- "MS Submaximal Exercise Test – No Stim – Adult"



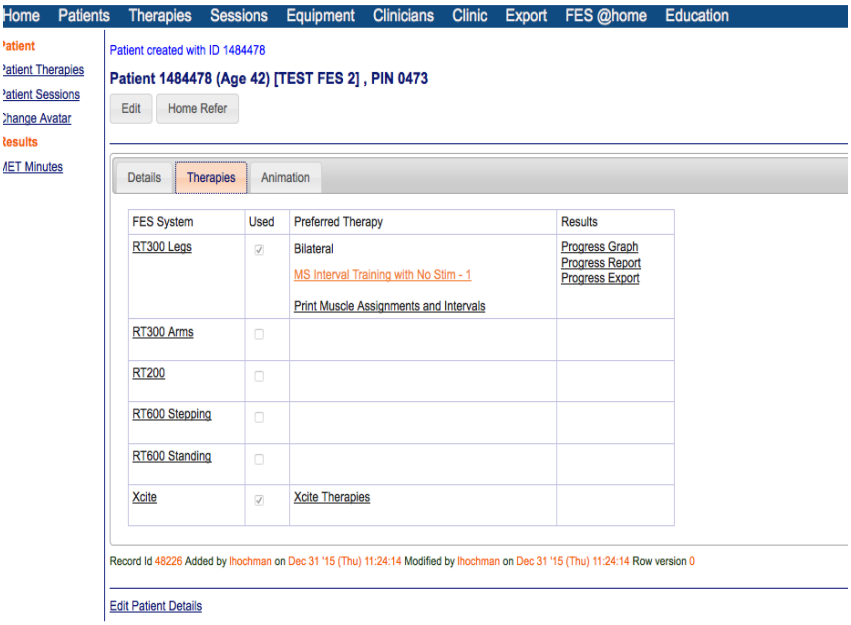
i. At the bottom on the screen click “SAVE”



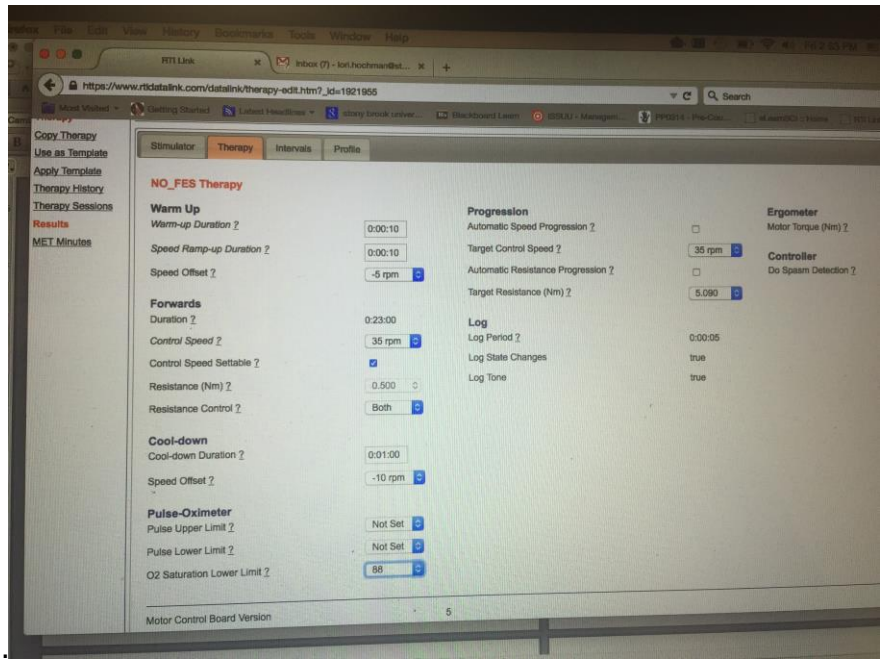
j. After you save, the following screen will appear



k. Click on the “Therapies” tab at the top and Click on “MS Submaximal Exercise Test- No Stim - 1”



l. Under Therapy, please insert Pulse Upper Limit ((HR $_{max}$ = 220 – age x .85) (e.g. HR $_{max}$ = 220 – 42 x .85= 151) and Lower Limit as 10 bpm below baseline HR



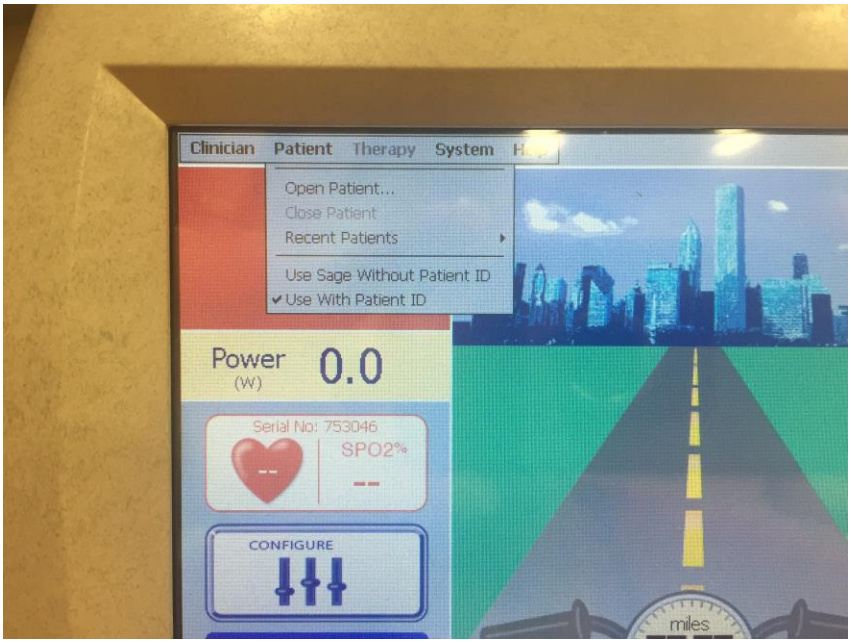
m. On the next screen click “Save”

RT300/SAGE CONTROLLER PROCEDURE

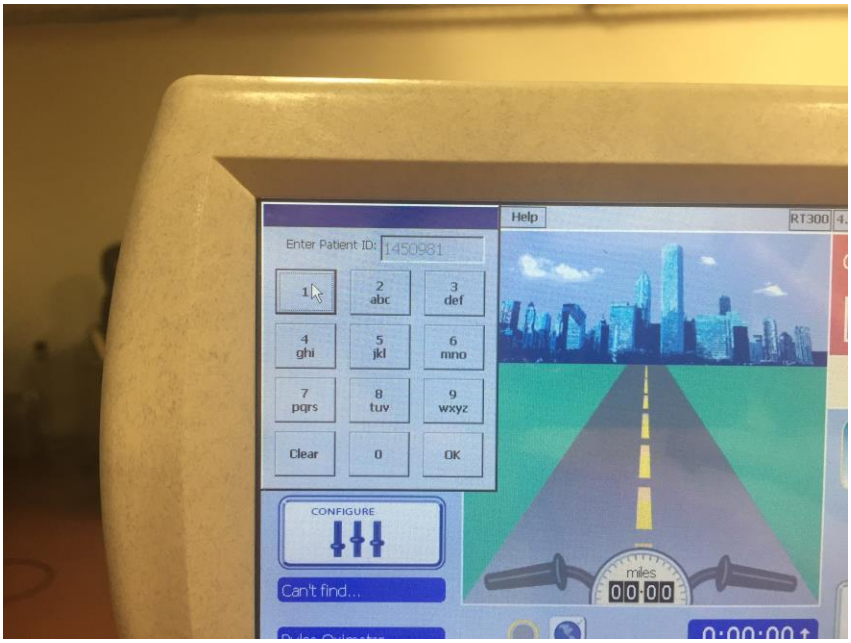
1. Plug in RT300 into outlet (screen will automatically turn on)
2. On the top left, tap on “Clinician” and then “Clinician Log In”
3. Enter Password “1776”
4. Look at globe on bottom of the screen. There should be a green check mark. If there is a red “X” than it is not connected to the network. (Try System—Synchronize)
5. If there is a red “X” then tap the globe.

Opening Patient

1. Click on “Patient” and Open Patient- (There will be a check mark next to “Use with Patient ID”)



1. Enter Patient ID, Click “OK



2. Enter Pin, Click “OK”

2. Click on “Therapies” and Click on “Leg – MS Submaximal Exercise Test – No Stim”

3. Clip Pulse Ox on participants ear and check connection (under System- Pulse Oximeter)
4. Set up participant on bike.

a. Position the participant in the chair with their legs will be positioned on the pedals and secured with Velcro strapping.
b. The bike and chair should be positioned to maintain 5-15 degrees of knee flexion when in the fully extended position of cycling. (note and write down the distance between the base of the bike and the front leg of the chair)
c. Adjust the height of the ergometer so that the rear of the participant's thigh does not press into the seat cushion as they cycle.
d. Add back support if need needed.
e. Adjust the seat height and depth by utilizing cushions in order to optimize positioning and cycling angles.

Participant Instructions for SXTT

"This part of the study will be obtaining your baseline exercise tolerance and your starting parameters for the study. You will be cycling for no more than 23 minutes. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle while keeping your control speed over 45 rpm. Every 3 minutes the resistance will increase. You may stop at any time due to fatigue or any other symptom exacerbation - including headache, change in vision, numbness, sudden paralysis, dizziness, or vertigo. I will stop the test if you report or experience chest pain, shortness of breath, wheezing, and leg cramps. I will also stop the test if your HR, pulse oxygen or BP are outside set parameters. Are you ready?"

Exercise Tolerance Testing Procedure (SXTT)

1. Participants will be asked to cycle at or above the 45 rpm target speed.
2. Participants will start with unloaded cycling and every 3 minutes the resistance will be increased by 3 Newton-meters (Nm) per stage (which is approximately 14 Watts per stage).

3. The SXTT will be discontinued when the participant reaches self-reported fatigue or if their vital signs fall outside a safe range. Maximal workload is defined at the last completed interval before termination.
4. HR and pulse oxygen will be measured in sitting at baseline and then recorded in during the last 5 seconds of each interval during clinical testing.
5. BP will be measured and recorded in sitting at baseline and during the last 45 seconds of each interval.
6. The RPE scale will be explained to participants at rest and recorded during the last 15 seconds of each interval.
7. Data from the exercise tolerance test will be recorded on the participant data sheet.

SXTT will be terminated if the participant:

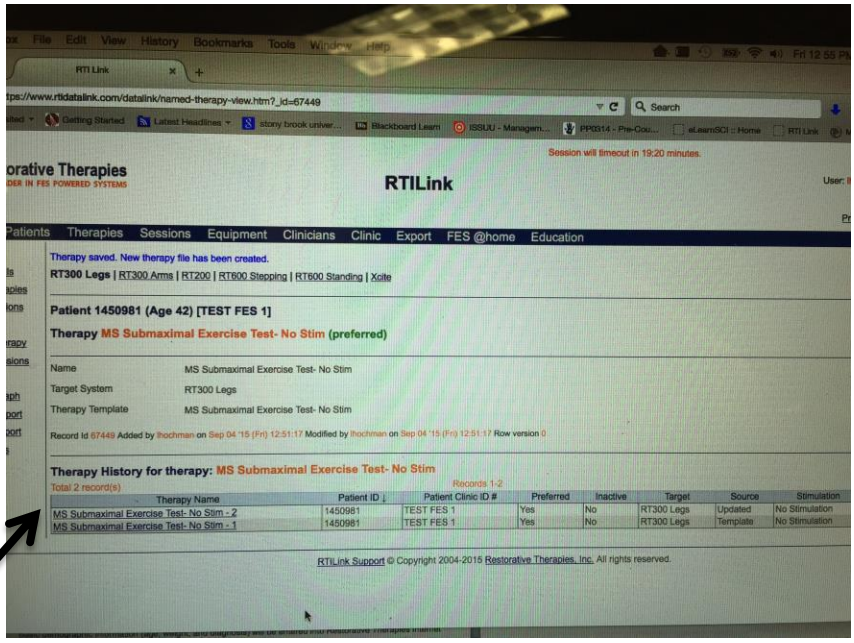
- Reports fatigue- participant expresses they can no longer pedal due to fatigue.
- Reaches 70% heart rate reserve which is 85% of age-predicted HR_{max}, (HR_{max} = 220 – age x .85).
- Fails to conform to exercise protocol, which for this study will be defined as falling 10 rpm below the target rpm speed of 35 for greater than 10 seconds.
- Has a hypotensive response- systolic blood pressure drops ≥ 10 mmHg from baseline
- Has a hypertensive response- systolic blood pressure > 250 mmHg and/or a DBP of > 115mmHg.
- Experiences symptom exacerbation- including headache, change in vision, numbness, sudden paralysis, dizziness, vertigo
- Reports chest pain, shortness of breath, wheezing, and leg cramps.

Training Protocols

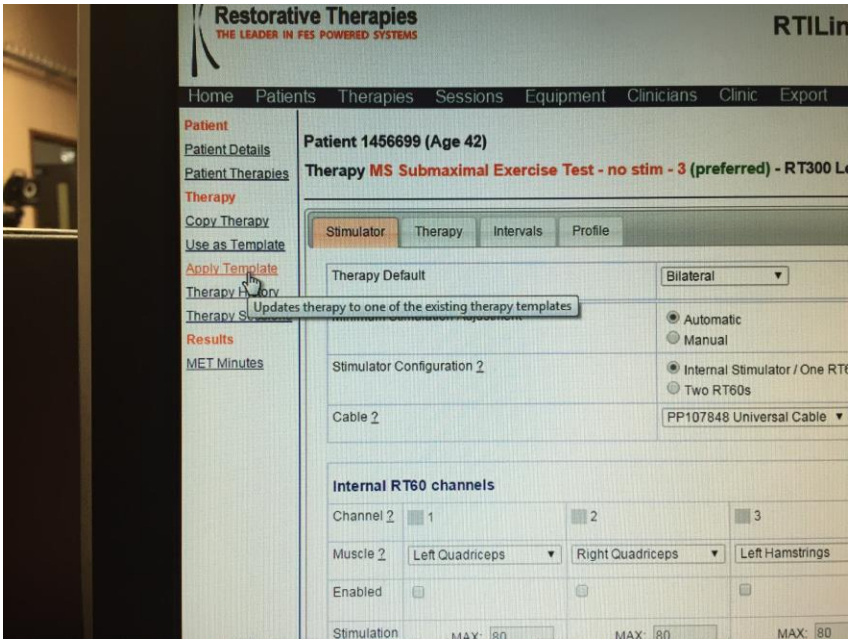
Participants will train for 45 minutes, three-days per week, for eight-weeks using an FES-LE cycle.

RTI Data Link Set-up for Baseline Stim Settings

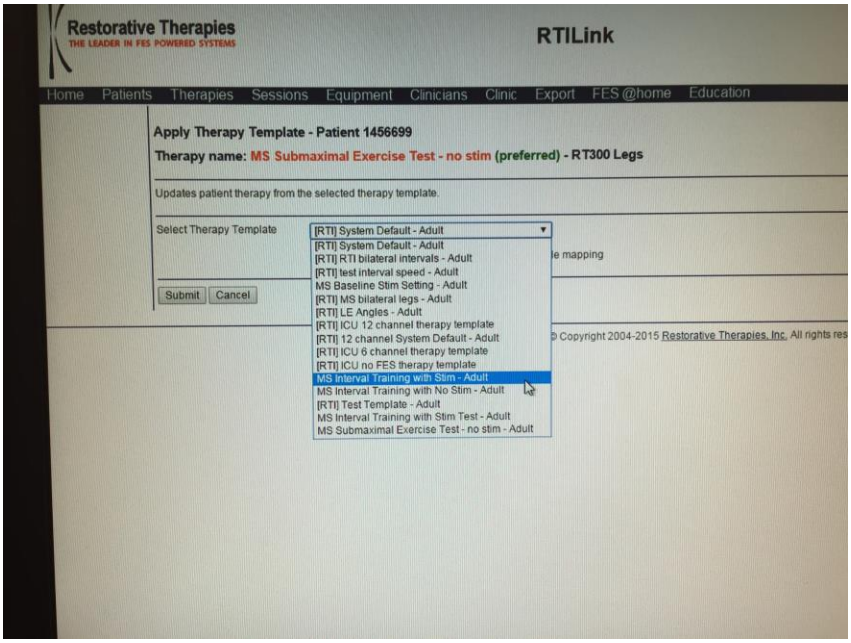
1. Go to: rtidatalink.com
2. Click on Patient on top bar
3. Click on the Patient ID # _____
4. On the left-hand side click "Patient Therapies" and select the last session which will be "MS Submaximal Exercise Test – No Stim – Adult"



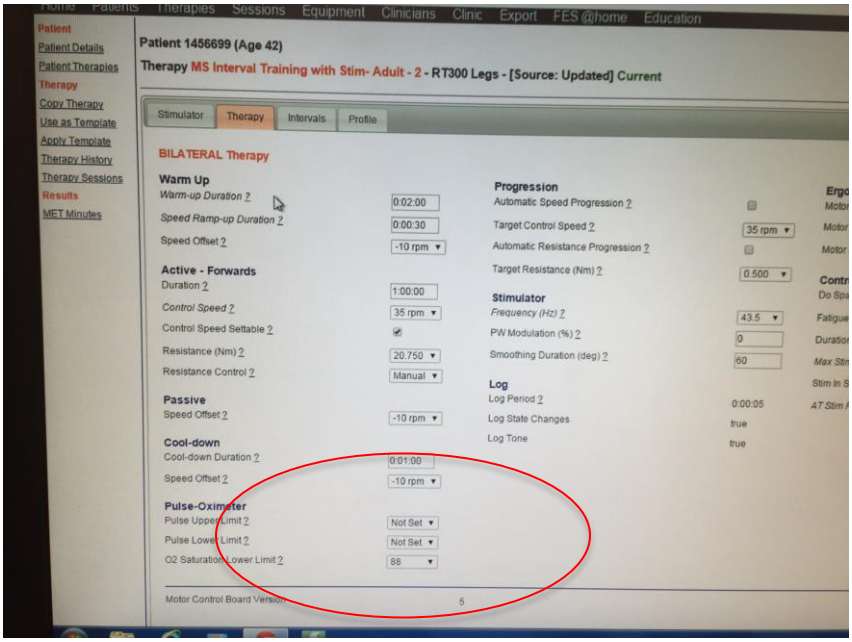
5. On the Left-hand side of screen click "Apply Template"



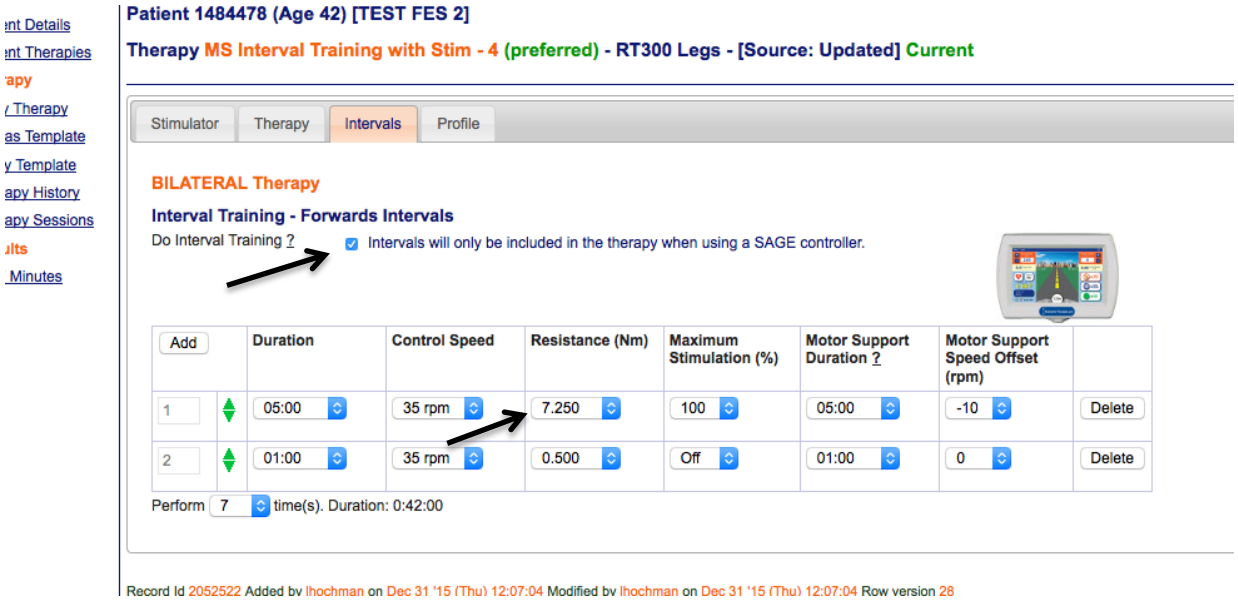
6. From the drop down menu select “MS Interval Training with Stim – Adult” (this puts the template under the patient therapies, but it will be under the name of the previous therapy MS Submaximal Exercise Test – No Stim – Adult and you will need to rename- see next step)



7. Go to Patient Therapies on left and select the first therapy and on the left-hand side **click "copy therapy"** and rename it "MS Interval training with Stim - Adult"
8. Open up the renamed template and set-up the following parameters under the "Therapy" tab
    a. Pulse upper limit (220-age X .85)
    b. Pulse lower limit (10 beats below baseline)
    c. O2 sat lower limit= 88%
    d. Ergometer: Change "Resistance" and "Target Resistance" to 60% of the max torque from the SXXT (e.g. If person stopped SXXT at 6NM then set starting torque at 3.6 NM)



9. Under the intervals tab- check of the intervals box and change the resistance to 60% of the SXXT. Then uncheck the box!!! Under the intervals tab make sure the box is not checked in order to turn the intervals off while you are doing the baseline stim setting.



FES GROUP

Opening Patient

1. Click on "Patient"
2. Open Patient- Enter Patient ID, Click "OK"
3. Enter Pin, Click "OK"
4. Click on "Therapies"
5. Click on "MS Interval Training with Stim"
6. Clip Pulse Ox on participants ear and check connection

For FES-LE cycling, stimulated muscles are standardized and include the gluteals, hamstrings, quadriceps, anterior tibialis, and gastrocnemius. Each participant will have their own set of electrodes that will be labeled with their participant number and will be stored at the research lab. Electrodes will be placed according to the guidelines outlined and participant morphology (see table below).

Electrode and Chair Set-up

1. Clean skin with alcohol and make sure it is dry prior to placing the electrodes on the skin. Before and after each training session, inspect skin for erythema, breakdown and/or irritation.

2. Check expiration dates on the electrodes prior to the commencement of training. **The manufacturer of the electrodes recommends that each electrode can be used for a maximum of 10-15 sessions.** If an electrode no longer adheres appropriately to the skin, discard the electrode and use a new electrode.
3. Label each participant's package of electrodes with the date and participant identification number.

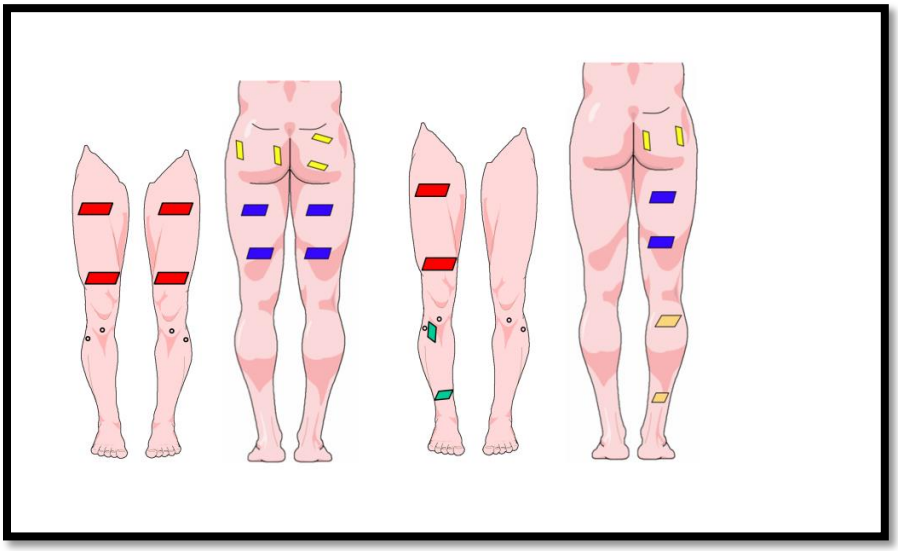
Muscle	Electrode Size	Location of placement
Quadriceps	3" X 4"	One electrode was placed a hand width above the knee centered on the belly of the quad and the second electrode was placed at least a hand width above the first electrode. For participants with a longer thigh length, it was placed higher on the quadriceps belly.
Hamstrings	3" X 4"	Electrodes were placed in line with the quadriceps electrodes, but on the back of the thigh and were centered in the middle of the hamstrings.
Gluteals	2" X 3.5"	One electrode was placed vertically with the top of the electrode parallel to the top gluteal cleft and the second electrode two-finger widths lateral to the first electrode.
Anterior Tibialis	2" X 3.5"	One electrode was placed proximally on the muscle belly and the second electrode was placed distally about 2/3 way down the shin.
Gastrocnemius	2" X 3.5	One electrode was placed horizontally across the calf, just below the knee and the second electrode was placed just distal to the gastrocnemius belly.

*The electrode sizes above were used as guidelines and individual adjustments were made based participant morphology.

4. Position the participant in the chair with their legs will be positioned on the pedals and secured with Velcro strapping.
5. The bike and chair should be positioned to maintain 5-15 degrees of knee flexion when in the fully extended position of cycling.
6. Adjust the height of the ergometer so that the rear of the participant's thigh does not press into the seat cushion as they cycle.
7. Add back support if need needed.

8. Adjust the seat height and depth by utilizing cushions in order to optimize positioning and cycling angles.
9. Secure foot strap in a cross pattern
10. Match electrode to the appropriate number lead from the bike.

#1	Left Quad
#2	Right Quad
#3	Left Hamstring
#4	Right Hamstring
#5	Left Glut
#6	Right Glut
RT 50A	Left Ant Tib
RT 50B	Right Ant Tib
RT 50C	Left Gastroc
RT 50 D	Right Gastroc



Initial Stimulation Settings

1. Pre-set Frequency= 43.5Hz for all muscle groups and **will not** be changed throughout the study.
2. Pre-set Pulse width = 250μsec for all muscle groups and will be adjusted as needed.
3. During this baseline session all muscle groups will be turned on at the same time while the participant passively cycles (i.e. motor of the cycle is moving their legs).
4. Amplitude will ramp up at 1% per second and the participant will be instructed to tell the investigator to limit the stimulation when the feel any of their muscles reach a point where the stimulation is starting to get uncomfortable.
5. The investigator will then adjust each muscle group individually to its maximal tolerable stimulation while the participant continues to passively cycle.
6. Adjust amplitude in increments of 1mA increments until a participant achieves a maximal but tolerable muscle contraction.
7. If a participant's tolerance to stimulation is reached before a detectable contraction is palpated decrease pulse width by 10μsec increments and then adjust amplitude by 1mA increments until a maximal muscle contraction to their tolerance is achieved.
8. The maximum level will be set at the value that has been determined to create a strongest tolerable motor response. If a participant is still unable able to achieve a muscle contraction due to discomfort, the highest stimulation parameters they reached will be used and parameters will be adjusted during training sessions as they accommodate to the stimulation.
9. All initial settings will be automatically saved in RTI Data Link.

Instructions to Participant

The following instructions will be used prior to the baseline stimulation set-up:

"You will be cycling for a short period of time in order for us to set-up your initial stimulation levels for your first training session. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle at a moderate effort level. The stimulation will slowly ramp up. When the stimulation gets uncomfortable in any of the muscle groups, please let me know and we will then adjust each muscle group. The goal is to create a strong, but tolerable muscle contract. This might take a few sessions for you to get used to the feeling"

FES Training Session Protocol

The participant's stimulation levels from their previous session will be used as starting parameters for each session. If during training sessions the participant can tolerate more stimulation, amplitude will be increased in 1 mA increments. If they reach the maximum amplitude level of 140ma and can tolerate more stimulation, pulse width will be increased by 10μsec increments.

Participants will experience a 2-minute warm-up period in which the ergometer's motor provides passive cycling and moves the participants' legs. The ergometer will then transition into "active mode" in which the electrical stimulation slowly ramps up to allow the individual to accommodate to the stimulation. During this period, the participant will receive stimulation while also using their own muscle power against a set resistance while working to maintain a set target speed of 45. In order to have participants working at a moderate intensity, starting resistance will be set at 60% of the maximal workload from the submaximal clinical exercise tolerance test (SXTT).

Participants will be encouraged to cycle continuously for at least 45 minutes using an interval training protocol. They will cycle for 5 minutes with stimulation and then 1 minute without stimulation with light (.5nm) resistance. This 5:1 (5 minutes of active cycling with stimulation: 1-minute cycling without stimulation) cycle will repeat 7 times

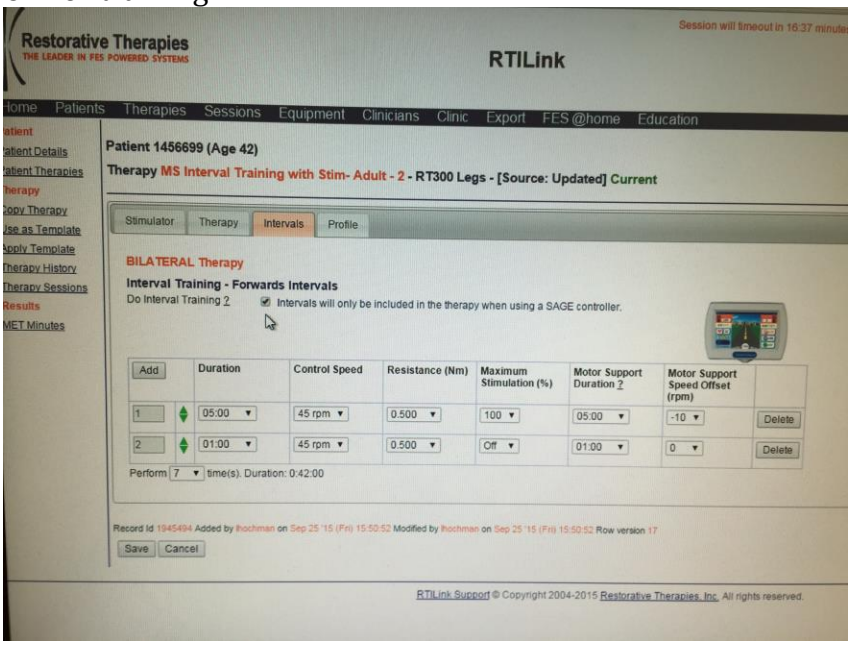
during the session. Participants will then receive a 1-minute cool-down at the end where they receive no stimulation and the cycles motor passively moves the lower limbs.

Since individuals in this study will have some degree of volitional control to cycle faster than their control speed, stimulation minimums/maximums will be set to the same level to ensure stimulation does not drop below the therapeutic level for each muscle group, therefore no matter how fast the participant cycles the stimulation will remain on during the 5-minute stimulation period. The RT300 can provide 'motor support" and the ergometer will be set for the participant to receive 'motor support' throughout the cycling period if they are not maintaining their target speed.

If at any time during training a participant reports fatigue and needs to discontinue cycling, stimulation will be discontinued, and the participant will continue the rest of their session in passive mode with the motor fully assisting their movement for the remainder of the therapy session. Once a participant can cycle the full 45 minutes using the 5:1 protocol, resistance will be increased by 5% increments every 3 sessions.

10. On the left-hand side click "Patient Therapies" and select the last session which will be "MS Interval Training – Stim"

11. Go to Patient Therapies on left and select the first therapy and on the left-hand side. Under the intervals tab make sure the box is checked in order to turn the intervals ON for training.



Instructions to Participant

The following instructions will be used prior to each training session:

> "You will be cycling for 45 minutes. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle at a moderate effort level. The stimulation will slowly ramp up over a 2-minute period to the stimulation levels we set during the previous session. If at any time the stimulation gets uncomfortable, please let me know and we can adjust the stimulation for each muscle group. You will cycle actively for 5 minutes and then receive a 1-minute break where the cycle will do all the work. This pattern of 5 minutes on, 1 minute off, will repeat 7 times during your training session. If at any time you experience fatigue, please let me know and you can take a break for up to 5 minutes and then continue where you left off. The cycle is set to go into a passive cycling mode if your speed falls 10 rpm below the set target speed of 45 rpm. The stimulation will be turned off and you will finish the remainder of the session allowing the bike to do all the work or you can stop the session."

During Cycling for 1st session explain to participant the feedback they receive from the screen:

1. Target Speed
2. Speed
3. Resistance
4. Asymmetry Display
5. Motor Support Indicator- Gray- motor support is not assisting the motion, Blue- motor support is enabled and being used.
6. Stimulation- present stimulation level

Cycling-only Protocol

Participants in this training group the will be set-up on the RT300 in the same manner as those in the FES training group, but they will not receive electrical stimulation nor wear stimulation pads; they will use the RT300 as an ergometer only. During the cycling-only phase, participants will cycle continuously for 45 minutes using an interval training protocol (5 minutes of active cycling: 1-minute passive cycling) at a set target speed of 45 rpm. This 5:1 cycle will repeat 7 times and then go into a 1-minute cool-down. Total active cycling time will be 35 minutes. If a participant needs a rest the cycle can go into passive mode and the motor of the cycle will provide full support. Once the participant is able to tolerate 45 minutes of cycling without rests at or above the specified target speed, the resistance will be increased in 5% increments every 3 sessions.

Participants in both groups will receive feedback from the screen on the bike during and after their treatment sessions, including distance traveled, right to left cycling symmetry, heart rate and oxygen saturation.

The following instructions will be used prior to each training session:

> "You will be cycling for 45 minutes. The first 2 minutes are a warm-up period in which the cycle is taking you through the cycling motion, so just relax and let the bike do the work. After the warm-up, start to actively cycle at a moderate effort level. You will cycle actively for 5 minutes and then receive a 1-minute break where the cycle will do all the work. This pattern of 5 minutes on, 1 minute off, will repeat 7 times during your training session. If at any time you experience fatigue, please let me know and you can take a break for up to 5 minutes and then continue where you left off. The cycle is set to go into a passive cycling mode if your speed falls 10 rpm below the set target speed of 45 rpm. If that occurs, will finish the remainder of the session allowing the bike to do all the work or you can stop the session."

RT 300 Features

The RT300 has several features that will be utilized during this study. One feature is the "control speed offset." If a participant's cycling speed falls below the target speed the ergometer's motor will take over for the remainder of the session and assist the participant. The control speed offset will be set at –10 rpm for all participants. The target speed for all participants will be 45 rpm and if a participant's speed falls below 35 rpm the ergometer's motor will take over and the cycle will finish the session in passive mode.

The SAGE stimulator also monitors electrode adherence and if an electrode falls off the system pauses and ceases stimulation and the motor turns off. An error message will be displayed on the screen telling the user which electrode needs to be checked. Once the electrode is secured, the session can continue.

If at any time a participant feels light-headed, nauseous, or dizzy during the training session or if their parameters fall outside the ACSM exercise guidelines, training will be discontinued for the remainder of the session.

All participants will be continuously monitored by a wireless heart rate and pulse oximeter with set parameters. Target HR goal for each participant will be set at 65% of their age-adjusted max HR (200 - age x .65). The maximum heart rate with set at 85% of age-adjusted max HR (220-age x .85). Participants will be encouraged to keep their HR within a 65% to 85% range. If a participant goes above their maximum heart for greater

than 10 seconds, the ergometer and session will be paused, and the participant will be given a 3-minute rest until their HR comes down to their target heart rate. If their HR does not come down into the appropriate range, they will continue the remainder of the session in the passive cycling mode. The minimum heart rate will be set at 5 bpm below the participants resting baseline to allow for normal HR variability that can occur from day-to-day.

If oxygen saturation (SPO_2) falls below 88% the session will be paused, and the participant will be instructed to perform deep breathing. Once the participant is back to their baseline SPO_2 saturation, they will be permitted to resume. They will be allowed a maximum of 5 minutes to achieve baseline. If they do not achieve their baseline within 5 minutes, they will continue the remainder of the session in the passive cycling mode.

Appendix H: Godin Leisure-Time Exercise Questionnaire

Date: _____ Participant #: _____

Godin Leisure-Time Exercise Questionnaire

1. During a typical **7-Day period** (a week), how many times on the average do you do the following kinds of exercise for **more than 15 minutes** during your free time (write on each line the appropriate number)?

Times Per Week

a) STRENUOUS EXERCISE
(HEART BEATS RAPIDLY) _____
(e.g., running, jogging, hockey, football, soccer, squash, basketball, cross-country skiing, judo, roller skating, vigorous swimming, vigorous long distance bicycling)

b) MODERATE EXERCISE
(NOT EXHAUSTING) _____
(e.g., fast walking, baseball, tennis, easy bicycling, volleyball, badminton, easy swimming, alpine skiing, popular and folk dancing)

c) MILD EXERCISE
(MINIMAL EFFORT) _____
(e.g., yoga, archery, fishing from river bank, bowling, horseshoes, golf, snow-mobiling, easy walking)

2. During a typical **7-Day period** (a week), in your leisure time, how often do you engage in any regular activity **long enough to work up a sweat** (heart beats rapidly)?

☐OFTEN

☐SOMETIMES

☐NEVER/RARELY

INSTRUCTIONS

In this excerpt from the Godin Leisure-Time Exercise Questionnaire, the individual is asked to complete a self-explanatory, brief four-item query of usual leisure-time exercise habits.

CALCULATIONS

For the first question, weekly frequencies of strenuous, moderate, and light activities are multiplied by nine, five, and three, respectively, the total weekly leisure activity is calculated in arbitrary units by summing the products of the separate components, as shown in the following formula:

Weekly leisure activity score = (9 × Strenuous) + (5 × Moderate) + (3 × Light)

The second question is used to calculate the frequency of weekly leisure-time activities pursued “long enough to work up a sweat” (see questionnaire).

EXAMPLE

Strenuous = 3 times/wk

Moderate = 6 times/wk

Light = 14 times/wk

Total leisure activity score = (9 × 3) + (5 × 6) + (3 × 14) = 27 + 30 + 42 = 99

Appendix I: Multiple Sclerosis Quality of Life–54 Instrument and Scoring Forms

Multiple Sclerosis Quality of Life

(MSQOL)-54 Instrument

For Further Information, Contact:

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INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:
(circle one number)

Excellent……1

Very good……2

Good……..3

Fair……..……..4

Poor……5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(circle one number)

Much better now than one year ago..... 1

Somewhat better now than one year ago…….2

About the same 3

Somewhat worse now than one year ago..... 4

Much worse now than one year ago 5

3-12. The following questions are about activities you might do during a typical day. Does **your health** limit you in these activities? If so, how much? (Circle 1, 2, or 3 on each line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not Limited at All
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several blocks	1	2	3
11. Walking one block	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

	YES	NO
13. Cut down on the amount of time you could spend on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious).

(Circle one number on each line)

	YES	NO
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all.....1

Slightly 2

Moderately.....3

Quite a bit 4

Extremely.....5

Pain

21. How much **bodily** pain have you had during the **past 4 weeks**?

(circle one number)

None 1

Very mild..... 2

Mild 3

Moderate..... 4

Severe 5

Very severe..... 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(circle one number)

Not at all..... 1

A little bit 2

Moderately..... 3

Quite a bit 4

Extremely..... 5

23-32. These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**... (Circle one number on each line)

	All of the Time	Most Of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

(circle one number)

All of the time.....1

Most of the time.....2

Some of the time 3

A little of the time.....4

None of the time.....5

Health in General

34-37. How TRUE or FALSE is each of the following statements for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks...**

(Circle one number on each line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the last 4 weeks only.**

How much of a problem was each of the following for you **during the past 4 weeks?**

(Circle one number on each line)

MEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Difficulty getting or keeping an erection	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

(Circle one number on each line)

WOMEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks**?

(circle one number)

Very satisfied..... 1

Somewhat satisfied..... 2

Neither satisfied nor
dissatisfied 3

Somewhat dissatisfied 4

Very dissatisfied..... 5

51. During the **past 4 weeks**, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbors, or groups?

(circle one number)

Not at all 1

Slightly..... 2

Moderately 3

Quite a bit..... 4

Extremely 5

52. During the **past 4 weeks**, how much did *pain* interfere with your enjoyment of life?

(circle one number)

Not at all 1

Slightly..... 2

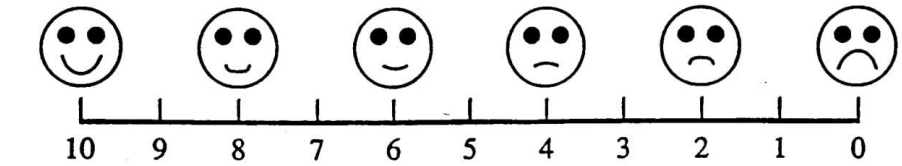
Moderately 3

Quite a bit..... 4

Extremely 5

53. Overall, how would you rate your own quality-of-life?

Circle one number on the scale below:



10 9 8 7 6 5 4 3 2 1 0

Best Possible Quality-of-Life

Worst Possible Quality-of-Life

As bad as or worse than being dead

54. Which best describes how you feel about your life as a whole?

(circle one number)

Terrible 1

Unhappy 2

Mostly dissatisfied 3

Mixed - about equally satisfied and dissatisfied 4

Mostly satisfied 5

Pleased 6

Delighted 7

Scoring Forms for Multiple Sclerosis Quality of Life (MSQOL) -54

Table 1
MSQOL-54 Scoring Form

Table 2
MSQOL-54 Physical Health Composite Score

Table 3
MSQOL-54 Mental Health Composite Score

Table 1

MSQOL-54 Scoring Form

Scale/Item Number	Response 1	2	3	4	5	6		Subtotal	Final Score 0-100 point scale
Physical Health									
3.	0	50	100					_____	
4.	0	50	100					_____	
5.	0	50	100					_____	
6.	0	50	100					_____	
7.	0	50	100					_____	
8.	0	50	100					_____	
9.	0	50	100					_____	
10.	0	50	100					_____	
11.	0	50	100					_____	
12.	0	50	100					_____	
							Total:	_____ ÷ 10 =	_____
Role limitations due to physical problems									
13.	0	100						_____	
14.	0	100						_____	
15.	0	100						_____	
16.	0	100						_____	
							Total:	_____ ÷ 4 =	_____
Role limitations due to emotional problems									
17.	0	100						_____	
18.	0	100						_____	
19.	0	100						_____	
							Total:	_____ ÷ 3 =	_____
Pain									
21.	100	80	60	40	20	0		_____	
22.	100	75	50	25	0			_____	
52.	100	75	50	25	0			_____	
							Total:	_____ ÷ 3 =	_____
Emotional well-being									
24.	0	20	40	60	80	100		_____	
25.	0	20	40	60	80	100		_____	
26.	100	80	60	40	20	0		_____	
28.	0	20	40	60	80	100		_____	
30.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____
Energy									
23.	100	80	60	40	20	0		_____	
27.	100	80	60	40	20	0		_____	
29.	0	20	40	60	80	100		_____	
31.	0	20	40	60	80	100		_____	
32.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____

Table 1 (cont.) Scale/Item Number	Response 1	2	3	4	5	6	Subtotal	Final Score 0-100 point

Health Perceptions

1.	100	75	50	25	0		_____	
34.	0	25	50	75	100		_____	
35.	100	75	50	25	0		_____	
36.	0	25	50	75	100		_____	
37.	100	75	50	25	0		_____	
						Total:	_____ ÷ 5 =	_____

Social function

20.	100	75	50	25	0		_____	
33.	0	25	50	75	100		_____	
51.	100	75	50	25	0		_____	
						Total:	_____ ÷ 3 =	_____

Cognitive function

42.	0	20	40	60	80	100	_____	
43.	0	20	40	60	80	100	_____	
44.	0	20	40	60	80	100	_____	
45.	0	20	40	60	80	100	_____	
						Total:	_____ ÷ 4 =	_____

Health distress

38.	0	20	40	60	80	100	_____	
39.	0	20	40	60	80	100	_____	
40.	0	20	40	60	80	100	_____	
41.	0	20	40	60	80	100	_____	
						Total:	_____ ÷ 4 =	_____

Sexual function*

46.	100	66.7	33.3	0			_____	
47.	100	66.7	33.3	0			_____	
48.	100	66.7	33.3	0			_____	
49.	100	66.7	33.3	0			_____	
						Total:	_____ ÷ 4 =	_____

Change in health

2.	100	75	50	25	0			_____

Satisfaction with sexual function

50.	100	75	50	25	0			_____

	Response						
Overall quality of life	**1**	**2**	**3**	**4**	**5**	**6**	**7**
53.	(multiply response by 10)						
54.	0	16.7	33.3	50	66.7	83.3	100

		_____	
		_____	
Total:		_____ ÷ 2 =	_____

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that if not every item within a given scale has been answered. For example, if item 38 in the Health Distress scale was left blank and the other 3 items in the scale were answered, then the "Total" score for Health Distress would be divided by '3' (instead of '4') to obtain the "Final Score."

* Males and females can be combined in the analysis even though question 47 is different for the two groups. The scale scores can also be reported separately for males and females.

Table 2
Formula for calculating MSQOL-54 Physical Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Physical function	_____	x	.17	=	_____(a)
Health perceptions	_____	x	.17	=	_____(b)
Energy/fatigue	_____	x	.12	=	_____(c)
Role limitations - physical	_____	x	.12	=	_____(d)
Pain	_____	x	.11	=	_____(e)
Sexual function	_____	x	.08	=	_____(f)
Social function	_____	x	.12	=	_____(g)
Health distress	_____	x	.11	=	_____(h)

PHYSICAL HEALTH COMPOSITE: Sum subtotals (a) through (h) = _____

Table 3
Formula for calculating MSQOL-54 Mental Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Health distress	_____	x	.14	=	_____(a)
Overall quality of life	_____	x	.18	=	_____(b)
Emotional well-being	_____	x	.29	=	_____(c)
Role limitations - emotional	_____	x	.24	=	_____(d)
Cognitive function	_____	x	.15	=	_____(e)

MENTAL HEALTH COMPOSITE: Sum subtotals (a) through (e) = _____

Appendix J: Modified Fatigue Impact Scale

MODIFIED FATIGUE IMPACT SCALE (MFIS)

Following is a list of statements that describe how fatigue may affect a person. Fatigue is a feeling of physical tiredness and lack of energy that many people experience from time to time. In medical conditions like MS, feelings of fatigue can occur more often and have a greater impact than usual. Please read each statement carefully, and then circle the one number that best indicates how often fatigue has affected you in this way during the past 4 weeks. (If you need help in marking your responses, tell the interviewer the number of the best response.) Please answer every question. If you are not sure which answer to select, please choose the one answer that comes closest to describing you. The interviewer can explain any words or phrases that you do not understand.

Because of my fatigue during the past 4 weeks....

	Never	Rarely	Sometimes	Often	Almost Always
1. I have been less alert.	0	1	2	3	4
2. I have had difficulty paying attention for long periods of time.	0	1	2	3	4
3. I have been unable to think clearly.	0	1	2	3	4
4. I have been clumsy and uncoordinated	0	1	2	3	4
5. I have been forgetful	0	1	2	3	4
6. I have had to pace myself in my physical activities.	0	1	2	3	4
7. I have been less motivated to do anything that requires physical effort.	0	1	2	3	4
8. I have been less motivated to participate in social activities.	0	1	2	3	4
9. I have been limited in my ability to do things away from home.					
10. I have had trouble maintaining physical effort for long periods.					

	Never	Rarely	Sometimes	Often	Almost Always
11. I have had difficulty making decisions.	0	1	2	3	4
12. I have been less motivated to do anything that requires thinking.	0	1	2	3	4
13. my muscles have felt weak.	0	1	2	3	4
14. I have been physically uncomfortable.	0	1	2	3	4
15. I have had trouble finishing tasks that require thinking.	0	1	2	3	4
16. I have had difficulty organizing my thoughts when doing things at home or at work.	0	1	2	3	4
17. I have been less able to complete tasks that require physical effort.	0	1	2	3	4
18. my thinking has been slowed down	0	1	2	3	4
19. I have had trouble concentrating.	0	1	2	3	4
20. I have limited my physical activities.	0	1	2	3	4
21. I have needed to rest more often or for longer periods.	0	1	2	3	4

Appendix K: 12-Item MS Walking Scale

Date: _____ Participant #: _____

12-Item MS Walking Scale (MSWS-12)

Instructions: These questions ask about limitations to your walking due to MS during the past 2 weeks. For each statement, please circle the one number that best describes your degree of limitation. Please answer all questions even if some seem rather similar to others, or seem irrelevant to you.

In the past two weeks, how much has your MS…	Not at all	A little	Moderately	Quite a bit	Extremely
1. Limited your ability to walk?	1	2	3	4	5
2. Limited your ability to run?	1	2	3	4	5
3. Limited your ability to climb up and down stairs?	1	2	3	4	5
4. Made standing when doing things more difficult?	1	2	3	4	5
5. Limited your balance when standing or walking?	1	2	3	4	5
6. Limit how far you are able to walk?	1	2	3	4	5
7. Increased the effort needed for you to walk?	1	2	3	4	5
8. Made it necessary for you to use support when walking indoors (e.g., holding on to furniture, using a stick, etc.)?	1	2	3	4	5
9. Made it necessary for you to use support when walking outdoors (e.g., using a stick, a frame, etc.)?	1	2	3	4	5
10. Slowed down your walking?	1	2	3	4	5
11. Affected how smoothly you walk?	1	2	3	4	5
12. Made you concentrate on your waking?	1	2	3	4	5

Please check that you have circled ONE number for EACH question

Appendix L: Activities-specific Balance Confidence Scale

Date: _____ Participant #: _____

The Activities-specific Balance Confidence (ABC) Scale

Instructions to Participants:

For each of the following, please indicate your level of confidence in doing the activity without losing your balance or becoming unsteady from choosing one of the percentage points on the scale from 0% to 100%. If you do not currently do the activity in question, try and imagine how confident you would be if you had to do the activity. If you normally use a walking aid to do the activity or hold onto someone, rate your confidence as it you were using these supports. If you have any questions about answering any of these items, please ask the administrator.

For each of the following activities, please indicate your level of self-confidence by choosing a corresponding number from the following rating scale:

0% 10 20 30 40 50 60 70 80 90 100%
no confidence completely confident

"How confident are you that you will not lose your balance or become unsteady when you…
1.…walk around the house? ____%
2.…walk up or down stairs? ____%
3.…bend over and pick up a slipper from the front of a closet floor ____%
4.…reach for a small can off a shelf at eye level? ____%
5.…stand on your tiptoes and reach for something above your head? ____%
6.…stand on a chair and reach for something? ____%
7.…sweep the floor? ____%
8.…walk outside the house to a car parked in the driveway? ____%
9.…get into or out of a car? ____%
10.…walk across a parking lot to the mall? ____%
11.…walk up or down a ramp? ____%
12.…walk in a crowded mall where people rapidly walk past you? ____%
13.…are bumped into by people as you walk through the mall?____%
14.… step onto or off an escalator while you are holding onto a railing?

____%
15.… step onto or off an escalator while holding onto parcels such that you cannot hold onto the railing? ____%
16.…walk outside on icy sidewalks? ____%

Appendix M: Rage of Perceived Exertion Scale

Rate of Perceived Exertion Scale

0 - Nothing at all

0.5 - Just noticeable

1 - Very light

2 - Light

3 - Moderate

4 - Somewhat heavy

5 - Heavy

6

7 -Very heavy

8

9

10 -Very, Very heavy

Appendix N: Submaximal Clinical Exercise Tolerance Test

Date: _____ Participant #: _____

Submaximal Clinical Exercise Tolerance Test
Target Speed: 40 rpm

Interval	Duration (minutes)	Workload Nm (Watts)	RPE	HR	Pulse Ox	BP
Unloaded Pedaling	2	0 Nm				
1	2	3 Nm (12.6)				
2	2	6 Nm (25.1)				
3	2	9 Nm (37.7)				
4	2	12 Nm (50.3)				
5	2	15 Nm (62.8)				
6	2	18 Nm (75.4)				
7	2	21 Nm (88)				
8	2	24 Nm (100.5)				
9	2	27 Nm (113.1)				

*2-minute passive cool-down (cycling below 40 rpm) will be instituted once a participant reaches their threshold.

Conversion of Watts into Nm
Nm = kW x 9549/rpm

Appendix O: TUG Within group differences from BTS G-Walk based on the mixed-effect model

Table 0-1 TUG Within group differences on phase durations based on the mixed-effect model

TUG- Sit to Stand Phase Duration (s)	FES Cycling	Cycling Only
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**0.05**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**0.01**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**0.001**
TUG- Stand to Sit Phase Duration (s)	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**0.04**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
TUG- Mid-turning Phase Duration (s)	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**0.05**
Baseline to Post-intervention	**0.02**	**NS**
Baseline to Follow-up	**0.001**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
TUG- End-turning Phase Duration (s)	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**

Abbreviations: TUG = Timed Up and Go, s = seconds, FES = Functional Electrical Stimulation, NS = Not Significant

Appendix P: 6MWT Within group differences on spatiotemporal gait parameters based on the mixed-effect model

Table 0-2 6MWT Within group differences on spatiotemporal parameters based on the mixed-effect model

6MWT- Stride Length-Left (m)	FES Cycling	Cycling Only
Baseline to Mid-point	**NS**	**0.04**
Baseline to Post-intervention	**NS**	**0.01**
Baseline to Follow-up	**NS**	**0.001**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
6MWT- Stride Length-Right (m)	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**0.03**
Baseline to Post-intervention	**NS**	**0.01**
Baseline to Follow-up	**NS**	**0.001**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
6MWT- Step Symmetry[d]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
6MWT- Double-Support- Left[e]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**0.05**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**0.04**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
6MWT- Double-Support- Right[e]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**0.05**	**NS**
Post-intervention to Follow-up	**NS**	**NS**

Appendix Q: Table 0-2 T25FW Within group differences on spatiotemporal parameters based on the mixed-effect model

Table 0-3 T25FW Within group differences on spatiotemporal parameters based on the mixed-effect model

T25FW- Stride Length-Left (m)	FES Cycling	Cycling Only
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
T25FW - Stride Length-Right (m)	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
T25FW - Step Symmetry[d]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**0.04**	**NS**
T25FW - Double-Support- Left[e]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**0.05**	**NS**
T25FW - Double-Support- Right[e]	**FES Cycling**	**Cycling Only**
Baseline to Mid-point	**NS**	**NS**
Baseline to Post-intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Mid-point to Post-intervention	**NS**	**NS**
Mid-point to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**

Appendix R: Quality of Life within group differences based on the mixed effect Model

Table 0-4 MSQOL-54, MFIS, MSWS-12, and ABC Within group differences based on the mixed-effect model

MSQOL-54 Physical Composite	FES Cycling	Cycling Only
Baseline to Post-Intervention	**0.01**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MSQOL-54 Mental Composite	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**0.05**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MSQOL-54 Overall Quality of Life	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**0.005**	**NS**
Baseline to Follow-up	**0.004**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MFIS-Total	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**0.03**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MFIS-Cognitive	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**0.04**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MFIS-Physical	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MFIS-Psychosocial	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
MSWS-12	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**
ABC	**FES Cycling**	**Cycling Only**
Baseline to Post-Intervention	**NS**	**NS**
Baseline to Follow-up	**NS**	**NS**
Post-intervention to Follow-up	**NS**	**NS**